

42nd Pancreas Club Abstract Posters

Listing by Corresponding Author. Full listing of authors and institutions will be in the final program book distributed at the meeting with full abstract. Poster numbers and list may change slightly. As of 4/18/08.

Abstracts indicated with * will have a invited Professor to discuss the poster with the authors and registrants during the Poster Viewing Session at 11:00 am.

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Poster #1: **PANCREATIC ADENOCARCINOMA WITH ISOLATED LOCAL VENOUS INVASION: DOES SURGICAL RESECTION CONFER A SURVIVAL BENEFIT?**

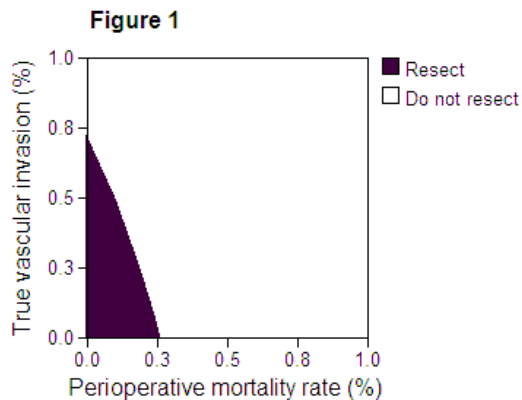
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BACKGROUND: Benefit from pancreaticoduodenectomy (PD) combined with superior mesenteric-portal vein (SMV-PV) resection in the management of pancreatic adenocarcinoma with local venous invasion remains controversial.

METHODS: Using formal decision analysis, we compared outcomes associated with PD plus SMV-PV resection (group I) versus those achieved using palliative chemoradiotherapy without resection (group II) when applied to patients with pancreatic adenocarcinoma with isolated local venous invasion. Individual studies were identified using MEDLINE. A total of 2,144 group I and 709 group II patients were evaluated. Patients with arterial invasion or distant metastases were excluded.

RESULTS: Group I patients had a 40% higher 1-yr survival rate ($p < 0.0001$) than group II patients. 1-way sensitivity analyses indicated that the robustness of this finding is contingent on two parameters (perioperative mortality rate and the percentage of cases in which true venous invasion by cancer is documented histologically). In the studies we evaluated, median perioperative mortality was 3.6% (range, 0 – 29%), and the median percentage of cases with true venous invasion was 63.6% (range 2.9 – 100%)

We then conducted a 2-way sensitivity analysis to evaluate the impact of varying these two parameters on whether surgical resection yields a higher 1-year survival rate than palliative treatment (Figure 1). The shaded portion of the figure (lower perioperative mortality rate and lower percentage of cases with true venous invasion) represents the area for which resection confers a higher 1-year survival than palliative treatment. The unshaded portion of the figure represents the area for which resection confers a lower 1-year survival rate than palliative treatment.



CONCLUSIONS: Our analysis suggests that pancreaticoduodenectomy with SMV-PV resection may confer a survival advantage over non-resectional palliation in select patients believed to have pancreatic adenocarcinoma with local venous invasion. Given the difficulty of identifying true vascular invasion preoperatively, these procedures should be done only if low perioperative mortality rates can be achieved.

Poster #2: **DIAGNOSTIC UTILITY OF CYST FLUID CEA ANALYSIS FOR PANCREATIC CYSTS: RESULTS FROM 110 PATIENTS TREATED AT A SINGLE INSTITUTION.**

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Background: Elevated cyst fluid CEA levels (>200 ng/ml) have been reported to be highly diagnostic of mucinous cystic neoplasms of the pancreas.

Methods: We identified 110 patients with cystic neoplasms of the pancreas who were treated at our institution between 2001 and 2007 and who had undergone endoscopic ultrasound and fine needle aspiration. All patients had cyst fluid CEA measured. Patient demographics, imaging studies, cyst characteristics, pathology, and treatment variables were recorded. The positive and negative predictive values (PPV and NPV) of an elevated cyst fluid CEA (CEA > 200 ng/ml) for detecting a mucinous cyst were calculated from patients who had pathologically proven diagnosis. The outcome of patients with an elevated cyst fluid CEA who were not resected was documented.

Results: A pathologically proven diagnosis was obtained in 44 patients. Within this group of patients, 11 had a cyst fluid CEA <200ng/ml and 33 had a cyst fluid CEA >200ng/ml. The NPV and PPV of cyst fluid CEA (>200 ng/ml and ≤200 ng/ml) for mucinous cystic neoplasms was 75% (25/33) and 72% (8/11). The degree of elevation in cyst fluid CEA was not associated with the degree of dysplasia within the mucinous lesion. An additional 21 patients with cyst fluid CEA > 200 were observed (mean CEA: 3847ng/ml; range 497 – 16000). Of these patients, 14 patients have greater than one year follow-up with median follow-up of 39 months (range 20-89 months). The average size of these non-resected lesions was 2.0 cm. None of these patients have experienced radiographic change or other findings suggestive of invasive disease.

Conclusions: In this study cyst fluid CEA of > 200 ng/ml was found to have a PPV of 75% and NPV of 72% for mucinous neoplasms of the pancreas and the degree of elevation was not associated with degree of dysplasia. Better markers for dysplasia are necessary to aid in operative selection as patients with early lesions may be followed safely.

Poster #3: **DOES SURGERY STILL PLAY A ROLE IN THE TREATMENT OF SEVERE ACUTE PANCREATITIS?**

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Introduction: Guidelines recommend fine needle aspiration (FNA) in patients with severe acute pancreatitis (SAP) and signs of sepsis. Infected necrosis is an indication for surgery. In our department different treatment strategies were applied over the last years.

Methods: From 09/2003 until 12/2007 patients with SAP were prospectively collected (group 1) and were compared to a retrospectively analyzed group treated from 03/2000 until 08/2003 where patients with SAP received FNA according to guidelines. Patients with positive FNA were analyzed in group 2. Prognostic and clinical parameter did not differ between groups. Patients of group 1 were initially treated conservatively. Progressive organ failure or increased demand of catecholamines was an indication for surgery.

Results: 49 FNAs and 144 operations were performed in 20 patients of group 2. Total mortality was 45%. 24 consecutive patients of group 1 underwent significantly less operations (35), and FNA was rarely performed. 12 patients were treated conservatively. Total mortality was significantly lower with 8.3%. The main finding of this clinical observation study is that patients who are operated on the basis of a positive FNA during the first 3 weeks of SAP had a mortality of 45%. In comparison, mortality could be reduced to 8.3% in patients with comparable severity of the disease by a conservative treatment regimen including a restriction of FNA.

Parameter	03/2000 until 08/2003 = group 2	09/2003 until 12/2007 = group 1	p
Number of patients	20	24	-
APACHE II upon admission	19.8 ± 1.7	16.1 ± 1.9	0.169
SOFA upon admission	8.7 ± 1.4	6.9 ± 1.0	0.312
Ranson	3.9 ± 0.3	3.9 ± 0.2	0.305
CTSI index CT	7.9 ± 0.5	7.9 ± 0.5	0.774
CRP on day 3 (mg/dl)	243 ± 21	291 ± 21	0.116
3-organ-failure	30 %	46 %	0.467
2-organ-failure	5 %	8.3 %	0.662
1-organ-failure	0 %	4.2 %	0.356
overall mortality	45 %	8.3 %	0.01

Conclusion: Sterile pancreatic necrosis should be treated conservatively. Any operation should be avoided within the first four weeks after admission. Therefore detection of infection is irrelevant as long as the patient remains clinically stable, even in the presence of MOF. Only if clinical condition deteriorates, operation is indicated. Infected pancreatic necrosis is no absolute indication for operation in clinically stable patients. However, conservative management of infected pancreatic necrosis has not been sufficiently evaluated yet and prospective studies are needed.

Poster #4: **BLOCKING ANGIOTENSIN II TYPE1 RECEPTOR TRIGGERS CELL CYCLE ARREST AND APOPTOTIC CELL DEATH IN HUMAN PANCREATIC CANCER CELLS**

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Introduction/Background: Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of adult cancer mortality in the United States. Its incidence and mortality rates are almost identical. Currently, there is no effective treatment for PDA. Surgery is the only curative option, but < 20% of all patients admitted with PDA undergo resection and at best, 25% of those survive for 5 years. Thus, there is an urgent need to identify novel and effective therapeutic strategies. We recently demonstrated that angiotensin II (AngII) type 1 receptor (AT1R) is functionally expressed in PDA tissues and may be involved in tumor angiogenesis. We also showed that AngII blockade by an AT1R blocker, losartan, potently reduces PDA cell survival. Here, we investigated the involvement of AT1R in PDA cell viability through examining the impact of its blockade on cell cycle and apoptosis and exploring the molecular mechanisms involved.

Methods: We used the human PDA cell line Panc10.01 in standard tissue culture conditions. PDA cell cycle was analyzed using flow cytometric analysis of DNA content by propidium iodide staining; apoptosis by annexin V-FITC and TUNEL staining; p53, p21^{WAF1}, Bax and bcl-2 mRNA and protein by real time PCR and Western blotting; caspase-3 activity by colorimetric assay. P53 promoter activity was evaluated by luciferase assay.

Results: Blocking AT1R by losartan (0.01-1mM) inhibited PDA cell growth dose-dependently and induced G₁ cell cycle arrest. This was associated with a dramatic increase in the expression of the cyclin-dependent kinase inhibitor p21^{WAF1} mRNA. Losartan also triggered a dose-dependent apoptosis, an effect that was associated with Bax upregulation, bcl-2 reduction, and activation of caspase-3. Losartan stimulated the expression of the tumor suppressor/pro apoptotic p53 gene and protein through induction of its promoter activity. Blocking p53 by an inhibitor, pifithrin- α , or siRNA restored the transcription of bcl-2 and partially suppressed the losartan-induced apoptosis but had no effect on p21^{WAF1} transcription or the cell cycle.

Conclusions: Our data demonstrate a previously undescribed involvement of AT1R in PDA cell survival, and suggest that the losartan-mediated induction cell cycle arrest and stimulation of different proapoptotic signaling pathways could represent the molecular basis of its action as a novel antineoplastic agent. Whether AT1R activation plays a role in the pathogenesis of PDA through suppressing p53 activity remains to be determined.

Poster #5: **THE NIGELLA SATIVA SEED EXTRACT, THYMOQUINONE, TRIGGERS APOPTOTIC CELL DEATH IN HUMAN PANCREATIC CANCER CELLS**

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Introduction/Background: Pancreatic ductal adenocarcinoma (PDA), one of the most lethal malignancies, is virtually therapy-resistant. Progression of PDA from its premalignant non-invasive lesions to a more malignant invasive phenotype is a multi-step process that depends on both genetic and epigenetic factors. This precursor period provides a window for cancer prevention by intervention with compounds that interfere with specific stages of neoplastic progression. Nigella sativa seed is an herb used in traditional medicine by many Middle Eastern countries to treat a broad array of diseases. Thymoquinone (Tq), the most abundant constituent of the seed essential oil extract has been demonstrated to have antineoplastic activities in different types of cancer. Tq also has cytoprotective effects that are mainly mediated through its antioxidant and anti-inflammatory activities. In this study, we investigated the antineoplastic potential of Tq in human PDA cells.

Methods: We used the human PDA cell line MiaPaca in standard tissue culture conditions. Cell cycle was analyzed using flow cytometric analysis of DNA content by propidium iodide staining; apoptosis was analyzed by TUNEL staining; p53, p21^{WAF1}, Bax and bcl-2 mRNA and protein by real time PCR and Western blotting. Caspase-3 activity was analyzed by a colorimetric assay. Histone 4 (H4) acetylation was analyzed by Western immunoblotting, Histone deacetylase (HDAC) activity by a colorimetric assay, and the expression of HDACs mRNA by PCR and QuantiGene assay.

Results: Addition of Tq (1-100 μ M) to PDA cells inhibited their proliferation and viability and induced partial G2 cycle arrest in a dose-dependent manner. Tq also induced accumulation of the cells in the sub G0/G1 phase indicating apoptosis. This was associated with induction of the tumor suppressor/pro apoptotic gene p53, and downregulation of the antiapoptotic bcl-2 gene. Tq dramatically increased the expression of p21 mRNA (~12-fold), independently of p53. Tq also induced epigenetic changes in PDA cells in the form of induction of H4 acetylation (lysine-12) and significant time-dependent downregulation of histone deacetylase activity. In addition, Tq reduced the transcription of HDACs 1, 2, 3 by 40-60%, but did not affect the expression of HDACs 4, 5, and 6.

Conclusions: This is the first report of a potent antineoplastic effect of Tq in PDA cells. Tq-mediated post-translational modification of histone acetylation, inhibition of HDACs activity and transcription, and induction of different proapoptotic signaling pathways could represent the molecular basis of Tq action as a novel antineoplastic agent.

Poster #6: **CLINICAL OUTCOME OF PATIENTS WITH INFECTION OF EXTRAPANCREATIC COLLECTIONS WITHOUT PANCREATIC PARENCHYMAL NECROSIS.**

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Introduction: Infection of pancreatic parenchymal necrosis is a major cause of morbidity and mortality in acute pancreatitis. Infection of extrapancreatic collections without pancreatic necrosis is a less known entity with few data on clinical course and outcome. In this study, we describe the clinical outcome of patients with infected extrapancreatic collections without accompanying pancreatic necrosis.

Methods: From a prospective database we retrospectively selected all patients with heterogeneous extrapancreatic collections with normal enhancement of the pancreatic parenchyma on initial contrast-enhanced computed tomography (CECT) (day 4 to 7 from onset of symptoms). None of these patients developed pancreatic necrosis later in the course of their disease, as evidenced by follow-up CT. A subgroup of these patients developed infection of extrapancreatic collections. Infection was diagnosed by positive culture of extrapancreatic fluid or extrapancreatic necrosis obtained by fine-needle aspiration, during the first radiological drainage or during the first operative intervention. Clinical outcome parameters were (multiple)organ failure, need for intensive care admission, need for radiological or operative intervention, length of hospital stay and mortality.

Results: One hundred eighty-seven patients with extrapancreatic heterogeneous acute collections and a normal enhancement of pancreas parenchyma were identified. Twenty-one (11%) of these patients developed infection of extrapancreatic collections. The female to male ratio was 1 versus 3, the median age was 54 (range; 28-82). The etiology of acute pancreatitis was biliary in 13 patients (62%), alcoholic in 5 (24%) and other causes in 3 patients (14%). On admission, the mean APACHE-II score was 7.8 and the highest mean C-reactive protein level in the first 48 hours was 289. Eleven patients (52%) developed organ failure during admission and 6 patients (29%) developed multiorgan failure. Fifteen patients (71%) were admitted to the intensive care with a mean stay of 28 days (range; 1-89). The mean length of hospital stay was 72 days (range; 13-172). The mean time until infection of extrapancreatic collections was diagnosed was 26 days (range; 6-72). All 21 patients required an intervention, either radiological drainage or operative necrosectomy, for suspicion of infected extrapancreatic collections and infection was confirmed by positive culture. Primary radiological drainage was performed in 17 patients of whom 9 patients subsequently also required operative intervention. Primary necrosectomy (without prior radiological drainage) was performed in 3 patients. The overall mortality in patients with extrapancreatic collections without pancreatic parenchymal necrosis was 6.5%. The mortality in patients with infection of extrapancreatic collections without pancreatic parenchymal necrosis was 29%.

Conclusion: Secondary infection of extrapancreatic collections in patients with acute pancreatitis without parenchymal necrosis leads to high mortality, comparable with mortality rates reported in the literature for infected pancreatic necrosis. The subgroup of patients without parenchymal necrosis, but with extrapancreatic collections, should therefore be monitored just as carefully as patients with pancreatic necrosis.

Poster #7: **TUMOR SIZE AT PRESENTATION IS THE KEY FOR MANAGING SEROUS CYSTADENOMA OF THE PANCREAS**

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Introduction/Background: Since serous cystic tumors (SCTs) are rarely malignant, their optimal management (surgical vs surveillance) is still unclear. A surgical approach is generally limited to symptomatic patients and in case of doubtful preoperative diagnosis. Aim of this work was to analyze clinical presentation, diagnostic work up, surgical vs nonoperative management and outcomes of patients with SCTs, evaluating a possible correlation between tumor-size at presentation and its growth rate during follow-up.

Methods: From February 1990 to April 2007, 241 pts with a clinico-radiological or pathological diagnosis of SCT were recorded in our database. Data regarding symptoms, treatment and outcomes were analyzed. Fifty-six patients with serial magnetic resonance cholangio pancreatography (MRCP) imaging performed over time were identified, and tumor growth rates were calculated for these cases.

Results: Mean age at presentation was 54 years and 81% of pts were female. 71% of pts were asymptomatic. The most common symptoms were abdominal pain (75,6%), acute pancreatitis (8,6%), weight loss (7,1%). On the basis of radiology, 117 asymptomatic pts (48,5%) underwent clinical observation (MRCP every 6-12 months) with a median follow up of 31 months. Overall, 94 patients underwent resection, with no mortality and an overall morbidity of 46%; final diagnosis at pathological examination was serous cystadenoma in all the cases. SCTs were located in pancreatic body-tail in 56.5% of resected patients and in 39% of those who underwent non-operative management ($P<0.05$). Regarding 56 patients with serial imaging, the median growth rate for tumors < 4 cm at presentation ($n=43$) was 0,096 cm/year, while it was 0,42 cm/year for those larger than 4 cm ($n=13$) ($P<0.05$).

Conclusions: In our experience SCTs are a benign neoplasm affecting preferentially female pts with symptoms in only 1/3 of the cases. SCTs larger than 4 cm are associated with significant growth over time. Therefore, surgical resection should be considered in symptomatic pts and in SCTs > 4 cm at presentation, considering the significant risk of tumor-growth. Non operative management is advisable in small SCTs with no symptoms.

Poster #8: **QUALITY OF LIFE IN LONG-TERM SURVIVORS AFTER PANCREATICOUDENECTOMY**

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Introduction/Background: Few data are available with respect to quality of life (QoL) in long-term survivors after pancreaticoduodenectomy (PD). Aim of this study is to evaluate QoL and long-term outcomes in patients who underwent PD for any reason between 1990 and 2003 at the Department of Surgery of the University of Verona with a minimum follow-up of 48 months.

Methods: Among 268 patients identified, 168 were still alive and were surveyed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), and with an Institutional questionnaire on long-term complications. Of the 168 surviving patients, 109 (65%) agreed to participate at a median of 7.5 years postoperatively.

Results: Pylorus-preserving pancreaticoduodenectomy (PPPD) was performed in 75% of cases; 56 patients (51.5%) had malignant neoplasms, 23 (21%) borderline tumors, and 30 (27.5%) benign neoplasms. Intraductal papillary mucinous neoplasms (IPMNs) was the most common indication for surgical resection (27.5%) followed by ductal adenocarcinoma (12%). Postoperative complications were recorded in 63 patients (58%). Overall, 75% of patients reported good scores in their perception of QoL. A significant decrease in QoL was found in patients with malignancy, with IPMNs, in survivors > 10 years, and in those who experienced postoperative complications ($P < 0.05$). Despite no significant differences in overall QoL perception, Whipple resection was more frequently associated with alterations of functional and symptomatic domains than PPPD. Overall, 55% of patients complained of steatorrhea, 40% of dumping syndrome, 54% of weight loss. Dumping syndrome was not significantly associated with Whipple procedure, while weight loss was more frequently observed after pancreateo-gastrostomy than pancreateo-jejunostomy. New endocrine insufficiency was found in 17% of cases. Recurrent abdominal pain was found in 41% of patients; these patients reported also a significant impairment of QoL.

Conclusions: PD is associated with acceptable QoL over time. However a careful long-term follow-up is necessary given the significant rate of exocrine insufficiency rate and impairments in digestive function. Patients with complicated postoperative course, malignancies, IPMNs and who underwent PD with pancreateogastric anastomosis are at higher risk of long-term complications and QoL impairments.

Poster #9 **LOOKING AT AN "EVIDENCED BASED FAST TRACK" PANCREATIC SURGERY: PRELIMINARY RESULTS OF RANDOMIZED CLINICAL TRIAL.**

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Background: In a previous study (1) we showed that the Amylase Value in Drains (AVD) after pancreatic resection was forward to be a predictive factor of postoperative pancreatic fistula (PF) development; in particular patients with a post-operative day one (POD1) median AVD of 10,000 U/L were at higher risk for PF, whereas patients without PF had a median AVD of 1222 U/L ($P < 0.001$). AVD in $POD1 > 5000$ U/L is the only significant predictive factor of PF development, therefore we established this cut-off as the "reference point" in PF prediction. At the same time others (2) demonstrated that early removal of drains on POD4 is an independent factor for reducing the incidence of abdominal complications, while patients with drains still in place after POD8 had a significantly higher incidence of abdominal complications ($P = 0.00003$) and PF ($P = 0.003$).

Aim: On this base we planned a randomized clinical trial in patients undergoing to pancreatic surgery, in our Institution. The cases with "low risk" (AVD in $POD1 < 5000$ U/L) were randomized to remove drains on POD3 (Group A, early drains removal) versus POD 5/6 (Group B) that was our usual removing time.

Patients and Methods: Between March 2007 to January 2008 we performed 157 major pancreatic resections. We prospectively randomized all 104 patients with AVD in $POD1 < 5000$ U/L (66% of all resections), in Group A ($n = 48$, 46%) and in Group B ($n = 56$, 54%). The outcome of the two groups was than compared.

Results: The two groups were homogeneous for type of resection (31 pancreaticoduodenectomies and 17 distal resections in the Group A versus 35 and 21 in Group B), sex, age, tissue texture and main duct diameter (< 3 mm or > 3 mm). There was no mortality in both groups. 13 patients had abdominal complications in Group B (23%) whereas nil in Group A ($p = 0.001$; OR 11); in particular, 10 PF (17%) were found in Group B versus 0 in Group A ($P = 0.002$; OR: 7), 12 (21%) fluid collections versus none ($p = 0.03$; OR 6) and 5 (9%) hospital readmissions versus 0 ($p = 0.06$; n.s). The pulmonary complications were higher in Group B (60% versus 32%; $p = 0.03$; OR: 6)

Conclusions: when AVD in $POD1$ is < 5000 U/L after pancreatic resection, the "early drains removal" ($POD3$) of surgical drains, significantly decreases the rate of abdominal and pulmonary complications, leading to a safe "fast track" policy.

1. Molinari et al Ann Surg. 2007;246:281-7
2. Kawai et al. Ann Surg. 2006; 244: 1-7

Poster #10: **INFECTIOUS COMPLICATIONS IN ACUTE PANCREATITIS; A PROSPECTIVE MULTICENTER STUDY**

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Background: Persistent organ failure and infectious complications are the major causes of death in acute pancreatitis. If strategies that aim to prevent infections are to be successful they should be implemented prior to diagnosis of infectious complications. Data is however lacking on the interval between admission and the diagnosis of infections in acute pancreatitis.

Methods: This prospective multicenter study in 15 Dutch hospitals included patients with a primary episode of acute pancreatitis from 2004-2007. Presence and timing of onset of bacteraemia, infected pancreatic necrosis, pneumonia, persistent (>48hr) organ failure and mortality was prospectively assessed.

Results: Of the 731 patients included, 61 patients (8 per cent) died, 25 of whom (41 per cent) in the first 14 days of admission. Infectious complications were diagnosed after a median of 8 days (interquartile range 3-20 days). Twenty per cent of these infections were diagnosed within the first 2 days of admission. In 154 patients with pancreatic necrosis, bacteremia was associated with increased the risk of infected necrosis (65 vs 38 per cent, $P = 0.002$). In 98 patients with infected necrosis, mortality was 2.5 times higher if bacteremia was present (40 vs 16 per cent, $P = 0.014$). After multivariate analysis the only variables associated with mortality were age, bacteraemia, Imrie score, and persistent organ failure.

Conclusions

Early mortality continues to play a significant role in acute pancreatitis. Infectious complications occur generally early in the course of acute pancreatitis, thus shifting the focus of prophylactic strategies to very early intervention.

Poster #11: **INTESTINAL BARRIER DYSFUNCTION IN A RANDOMIZED CLINICAL TRIAL OF PROBIOTIC PROPHYLAXIS IN ACUTE PANCREATITIS**

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Background Intestinal barrier dysfunction is thought to be associated with infectious complications, organ failure and mortality in acute pancreatitis. Several experimental studies have demonstrated that pre-treatment with probiotics abolishes barrier dysfunction. To date, no clinical study has reported a) a relationship between barrier dysfunction and the risk of infectious complications and b) a beneficial effect of probiotics on barrier dysfunction.

Methods During a randomised, double-blind, placebo-controlled trial on probiotic prophylaxis in patients with acute pancreatitis, intestinal permeability was assessed in 101 patients within 72 hours after admission and seven days thereafter by enteral administration of four polyethylene glycols (PEGs) with varying molecular weights (400, 1500, 4000 and 10000 kDa). PEG-recovery was determined by high performance liquid chromatography in 24-hour urine. Intestinal ischemia was assessed in 141 patients by measuring intestinal fatty binding acid protein (IFABP) concentration in urine collected 24-48 hrs after onset of probiotic or placebo treatment.

Results PEG-recovery was higher in patients that died (PEG 4000, $p=0.009$), developed organ failure (PEG 4000, $p<0.0001$) or developed bacteremia (PEG 4000, $p=0.001$) than in patients without these events. Probiotic prophylaxis had no detectable influence on intestinal permeability but IFABP concentrations in urine collected 24-48 hours after start of treatment, were higher in patients who received probiotics (median 362 vs 199 pg/ml; $p=0.02$). This effect was only seen in patients with organ failure. IFABP concentrations were higher in patients that developed organ failure ($p=0.008$), pancreatic necrosis ($p=0.001$), bacteremia ($p=0.03$) and infected necrosis ($p=0.01$).

Conclusions Intestinal permeability and ischemia early in acute pancreatitis were associated with mortality, organ failure, infected necrosis and bacteremia. Probiotic prophylaxis did not affect intestinal permeability but was associated with intestinal ischemia.

Poster #12: **SURGICAL RESECTION DOES NOT INCREASE SURVIVAL IN PATIENTS WITH METASTATIC PANCREATIC CANCER**

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Background: Surgical debulking of local-regional disease is associated with prolonged survival in patients with metastatic breast and ovarian cancers. The benefit of surgical resection in patients with metastatic pancreatic adenocarcinoma is unclear. We sought to identify the impact of surgical resection in patients diagnosed with metastatic pancreatic adenocarcinoma.

Methods: Through the California Cancer Registry, we identified all California residents diagnosed with invasive pancreatic adenocarcinoma between 1994 and 2002. The study population included all patients diagnosed at presentation with metastatic disease. Factors potentially impacting survival including age, gender, tumor characteristics, lymph node status, receipt of adjuvant therapy, and surgical resection were analyzed. Univariate survival analysis was performed by the Kaplan-Meier method. Multivariate analysis was performed using Cox regression analysis.

Results: 26,518 patients were identified, of which 11,663 (44%) were diagnosed with metastatic disease at presentation. Of these, 253 (2%) underwent pancreatic resection as part of their primary treatment. Median survival was longer for resected vs. unresected patients (7 mo. vs. 3 mo., $p < 0.001$). However, on multivariate analysis, after adjusting for patient demographics, tumor characteristics, extent of disease, and receipt of adjuvant therapy, surgical resection was not associated with any significant improvement in survival.

Conclusions: Surgical resection itself does not improve survival in patients with metastatic adenocarcinoma; apparent improvements in survival appear to reflect selection bias in surgical patients.

Poster #13: TUMOR MARKER-DIRECTED SELECTION INCREASES THE YIELD OF LAPAROSCOPY FOR PANCREATIC ADENOCARCINOMA: A CALL FOR SELECTIVE LAPAROSCOPY

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BACKGROUND: A significant proportion of patients with presumed resectable pancreatic cancer based on preoperative imaging are found to have unresectable disease at exploration. Laparoscopy has been advocated to identify these patients and spare them from unnecessary exploration, though the yield of routine laparoscopy is less than 25%. We have previously shown that serum CA19-9 is correlated with extent of disease. We therefore tested the hypothesis that CA19-9 could be used to select patients for diagnostic laparoscopy.

METHODS: From May 2003 to December 2007, 35 patients with confirmed or suspected pancreatic adenocarcinoma, were prospectively selected to undergo laparoscopy. Selection criteria included: 1) resectable tumor of the pancreatic head based on preoperative imaging (15 sensor CT with bolus intravenous contrast, and pancreatic thin cuts), and 2) elevated adjusted CA19-9 >150. Resectable disease was defined as tumor confined to the pancreas without vascular involvement (except portal vein), or distant metastases. Diagnostic laparoscopy consisted of inspection of the peritoneum and liver with biopsy of any abnormality; ultrasound and extensive dissection were not performed.

RESULTS: Of the 35 patients, one was excluded due to a diagnosis other than pancreatic adenocarcinoma (infected pseudocyst). Of the remaining 34 patients, the mean adjusted CA19-9 level was 1656 (range of 187 to 17,182). 15 patients (44%) were found to be unresectable during laparoscopy (13 liver metastases, 1 carcinomatosis, and 1 infiltration of the root of the mesentery). The remaining 18 (53%) underwent laparotomy for attempted resection (1 patient declined laparotomy). Of these, 8 (24% of total) had unresectable disease not identified on laparoscopy or imaging (6 with locally advanced disease precluding resection, and 2 with advanced nodal disease). 10 pts (29% of total) had resectable disease consistent with both their radiographic and laparoscopic findings, and. The sensitivity and specificity of laparoscopy in this set of patients with these criteria was 65% and 100% respectively, yielding an overall accuracy of 74% for selective laparoscopy.

CONCLUSIONS/DISCUSSION: Three quarters of all patients deemed resectable on imaging, but with abnormally high CA19-9 levels have advanced disease precluding curative resection. Laparoscopy identified 2/3 of these unresectable patients (46% of total), identifying a greater proportion of unresectable patients than previously observed in studies of routine laparoscopy. The yield of laparoscopy is higher when selectively applied to patients with an abnormally high CA19-9.

Poster #14: **THE PHENOTYPE OF FAMILIAL PANCREATIC NEOPLASIA**

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Screening with EUS and CT/MRCP can detect pancreatic neoplasia in asymptomatic high risk individuals (HRI). AIM: To determine the clinical, radiologic, and pathologic correlates of familial pancreatic neoplasia in HRI.

METHODS: HRI with at least 2 blood relatives with PC, PJS, and/or a BRCA2 mutation were screened with EUS and multi-detector CT(1998-2005) or EUS with MRI/MRCP (2005-2007) as part of our research studies or clinical screening program. Questionnaires and EUS and CT/MRCP results were recorded at baseline and follow-up. Annual surveillance was suggested. Gross and microscopic pathologic specimens from surgically-treated patients were evaluated by a single expert pathologist. Neoplastic lesions were counted and graded for dysplasia using international consensus classification systems. The density of pancreatic intraepithelial neoplasia (PanIN) was determined (total number of PanIN /total number of duct profiles).

RESULTS: 176 asymptomatic HRI (59% women, age 30-76) had screening EUS and either CT or MRCP. To date, follow-up was available on 77%. 19 patients underwent 24 operations for suspected pancreatic neoplasms (11 Whipple, 10 distal, 2 total pancreatectomy) detected at baseline or during surveillance (follow-up time median 5.4 years). HRI presented with cystic masses (n=16, 8 multiple) or solid masses (> 1 cm) or nodules (< 1 cm) (n=7, 2 multiple). 14 (64%) had chronic pancreatitis-like features with EUS. 14/24 resected pancreata contained intraductal papillary mucinous neoplasms (IPMN), multiple in 37%, size 5-20 mm; 2 patients had IPMN had high-grade dysplasia, the rest had moderate or low-grade dysplasia. 6 patients had incipient IPMN (larger than PanIN with finger-like papillae, size <1 cm), none with HGD, alone or with IPMN. 3 patients had single or multiple pancreatic endocrine neoplasms (PEN)(size 2-15 mm). One patient had an invasive PC without associated IPMN and another had 2 IPMN with multiple PanIN and microinvasive PC. 8/19 patients (42%) had either high grade IPMN or PanIN-3. 6 patients had PanIN-3 (1-14 lesions per pancreas), 4 larger lesions visualized by EUS. The median PanIN density for patients with EUS changes of chronic pancreatitis (> 4 features) was significantly greater than that for those that did not meet criteria (14.3% vs. 3.2%, p=.004). PanIN density was positively correlated with the number of EUS features (p=.0012). All cases with multifocal PanIN were associated with lobulocentric parenchymal atrophy. No patient under 45 years of age had a high grade or malignant neoplasm.

CONCLUSIONS: The phenotype of early pancreatic neoplasia includes multifocal PanIN with associated lobulocentric atrophy, single or multiple IPMNs, and/or endocrine neoplasms.

Poster #15: **COMPARISON OF HEALTH-RELATED QUALITY OF LIFE BETWEEN PREOPERATIVE AND POSTOPERATIVE STAGE AFTER PANCREATODUODENECTOMY.**

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Introduction: Health-related quality of life (hQOL) has turned to be an important clinical outcome to assess in the surgical practice. Moreover, it could play a relevant role in the decision-making work-up. Previous studies have shown hQOL results only in the postoperative period, without comparing the direct impact of the surgical procedure on the patient's perception of quality of life. The aim of this work is to analyze the effect of pancreatoduodenectomy in hQOL, comparing the preoperative vs. postoperative hQOL status.

Material and Methods A prospective single-center study was done during a 2-year period, comprising 43 patients (19 male, 24 female) who underwent classic pancreatoduodenectomy, with pathology-proven diagnosis of ductal adenocarcinoma (27.9%), ampullary adenocarcinoma (34.9%), other neoplasias (32.6%) and benign disease (4.7%). The 36-Item Short-Form Health Survey (SF-36) questionnaire was applied in the preoperative period and postoperative 1, 3, 6 and 12 months. Parametric and nonparametric-paired tests were done to determine differences in QOL scores during the clinical course. A comparison with the Mexican SF-36 norms was also done.

Results Significant differences in specific hQOL domains were found when comparing the preoperative stage vs. postoperative period (1, 3, 6 and 12 months). The general trend was towards improvement. (Table 1).

Table 1. HQOL differences compared to preoperative scores.
+ hQOL improvement above preoperative scores.

As expected, hQOL scores were below the SF-36 Mexican norms. However, hQOL differences decreased from the preoperative stage to the 12 months follow-up, even surpassing the Mexican norm scores in the general health perception (+17.2, p=0.0001) and social functioning (+1.3, p=0.04) domains at 12 months. No differences in hQOL were found among distinct pathological diagnosis.

SF-36 Item	1 month	P value	3 months	P value	6 months	P value	12 months	P value
Physical Functioning	26.5	0.0001	+7.4	0.4	+6.6	0.3	+15.9	0.08
Functioning Role	1.7	0.7	+11.8	0.1	+47.3	0.001	+59.7	0.001
Bodily Pain	0.5	0.9	+12.7	0.05	+17.4	0.01	+14.4	0.04
General Health Perception	+4.3	0.3	+9.4	0.1	+9.8	0.05	+12.8	0.02
Vitality	1.0	0.8	+7.3	0.1	+16.4	0.04	+15.6	0.009
Social Functioning	2.5	0.6	+20.3	0.01	+18.1	0.005	+21.1	0.03
Emotional Role	20.2	0.03	7	0.5	+22.2	0.1	+41	0.005
Mental Health	+5.1	0.1	+14.9	0.01	+13.8	0.004	+8.4	0.1

Poster #16: **RISK FACTORS FOR PANCREATIC LEAK FOLLOWING DISTAL PANCREATECTOMY**

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Introduction / Background: Pancreatic leak (PL) remains a major cause of postoperative morbidity in patients undergoing pancreatic resection. We sought to evaluate the incidence of and identify risk factors for the development of PL in patients undergoing distal pancreatectomy (DP) at a single high-volume institution.

Methods: All patients who underwent primary DP (excluding completion pancreatectomy and debridement) between 1/1/1984 and 7/1/2006 were identified. Data on demographics, clinicopathologic features, operative details, complications, and mortality were collected and analyzed. Chi-squared and multivariate logistic regression analyses were performed to identify risk factors for PL.

Results: In a cohort of 704 patients undergoing primary DP, the median age was 58 years, 45% were male, and 80% were white. The indications for DP were benign pancreatic neoplasm (34%), malignant pancreatic neoplasm (31%), other neoplasm (15%), chronic pancreatitis (14%), pseudocyst (3%), and trauma (3%). Concomitant splenectomy was performed in 89% of cases. The pancreatic remnant was sutured alone in 83%, stapled alone in 5%, and both stapled and sutured in 9% of cases. Ligation of the pancreatic duct was performed in 22% of cases. Perioperative mortality was <1%, but overall morbidity was 33%. PL requiring a change in clinical management was seen in 12% of cases. Development of PL was associated with an increase in perioperative mortality from 1% to 4% (P=0.04) and an increase in median length of stay from 7 to 10 days (P<0.001). Of those with PL, 35% required additional percutaneous drainage, but only 2% required reoperative intervention. Multivariate logistic regression analysis revealed that malignant neoplasm (odds ratio (OR) 1.3, P=0.29) and chronic pancreatitis (OR 1.6, P=0.12) as indications for DP did not change PL risk as compared to benign neoplasm. However, increased risk of PL was seen when DP was performed for trauma (OR 6.2, P=0.001) or pancreatic pseudocyst (OR 3.3, P=0.02). Tobacco use (OR 2.0, P<0.001) was associated with increased PL risk, while preoperative diabetes was associated with decreased risk (OR 0.33, P=0.003). Neither staple versus suture closure of the pancreatic remnant (OR 1.4, P=0.65) nor ligation of the pancreatic duct (OR 2.0, P=0.05) affected PL risk.

Discussion / Conclusion: This largest reported series of DP demonstrates that this procedure can be performed with low mortality but still carries a substantial risk of morbidity, particularly PL. DP for trauma or pancreatic pseudocyst significantly increases the risk of PL. In contrast to some previous studies, this analysis found that surgical management of the pancreatic remnant has no effect on the incidence of PL. These results emphasize the need for prospective randomized trials to evaluate strategies to reduce PL occurrence.

Poster #17: **PANCREATECTOMY WITH ISLET AUTO-TRANSPLANTATION FOR SEVERE CHRONIC PANCREATITIS**

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BACKGROUND Chronic pancreatitis (CP) is progressive and debilitating. Pancreatic resection can alleviate pain although the apancreatic state can cause “brittle” diabetes. Resection with islet auto-transplantation (IAT) resection decreases diabetes-related morbidity. Even if insulin independence is not obtained, patients who undergo IAT, diabetes related complications can be minimized.

AIM To evaluate treatment success and safety of pancreatic resection with islet auto-transplantation for chronic pancreatitis. To evaluate islet yield and diabetes related complications after pancreatic resection.

METHODS Patients with chronic pancreatitis who underwent pancreatectomy with IAT from April 2005 to December 2007 were evaluated in this retrospective case cohort study. Demographic, operative, islet cell, and follow-up data were collected by chart and database review. Subgroup analyses were performed on total pancreatectomy (TP) and pancreaticoduodenectomy (PD) patients.

RESULTS Twenty-seven patients (mean age 44 years) underwent 28 pancreatic resections with islet autotransplantation. Most were men (54%) and etiologies included alcohol abuse (35%), idiopathic (31%), and pancreatic divisum (23%). Salvage pancreatectomy was required in the seven (26%) patients who underwent previous pancreatic operations and an additional 14 (52%) had undergone endoscopic pancreatic stenting. All patients were taking narcotic medications and most had undergone celiac neurolysis. Mean preoperative glycosylated hemoglobin level was 5.7% (non-diabetic 3.5 – 5.5%) and no patients were on insulin. Preoperative c-peptide level was 2.7 (mean, normal .78 – 1.89 ng/ml). Preoperative Body Mass Index was 22 (mean, normal 18.5 – 25) and seven (25%) patients were less than 18 (underweight < 18.5). Mean operative time was 7.1 and 6.2 hrs, blood loss was 715 and 320 cc, and length of hospital stay was 10 and 10.7 days, for TP (n=21) and PD (n=7) patients, respectively. Complication rate was 56% and there was no mortality. Mean islet equivalents (IEQ) infused and IEQ per gram of pancreas were 82,100 and 2,750, respectively. Only 4 patients received over 200,000 islet equivalents. At 6 months, 60% of patients were free of narcotics and 20% had decreased their dosage. Mean c-peptide and glycosylated hemoglobin levels were 1.7 and 7.0%, respectively. Patient weight had decreased 13% (mean) despite all undergoing enzyme supplementation. There were no hypoglycemic complications or hospital admissions.

CONCLUSIONS

Pancreatic resection with IAT is safe and highly effective for the treatment of intractable pain associated with CP. Exocrine supplementation must be reinforced and feeding access may be indicated in order to decrease postoperative weight loss. Islet autotransplantation can eliminate hypoglycemic complications associated with the apancreatic state. Our relatively low islet yield is most likely due to advanced severity of CP, as reflected in borderline preoperative glycosylated hemoglobin levels. Earlier referral for definitive surgical evaluation may improve outcomes.

Poster #18: **PROTEOMIC ANALYSIS OF HUMAN PANCREATIC JUICE: CHARACTERISTICS AND CANCER-SPECIFIC FINDINGS**

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BACKGROUND Diagnostic or prognostic pancreatic cancer-specific biologic markers have not been identified. Mass spectrometry (MS) has not been widely applied to the evaluation of pancreatic cancer. Proteomic differences between benign and malignant pancreatic disease are unclear and not clearly documented. The largest proteomic series in the literature have only identified about 100 pancreatic juice proteins related to cancer. Identification of pancreatic juice cancer-specific proteins may aid in pre-operative screening and diagnosis. **AIM** To implement newly developed proteomic technology to identify characteristics of human pancreatic juice. To describe pancreatic juice protein differences between those with and without pancreatic cancer.

METHODS In this pilot study, we applied a novel two tier nano-LC-MS (MS) 2 analysis following depletion of the top 12 common serologic proteins (including albumin and IgG). Two separate mass spectrometry approaches were combined: low mass proteins were analyzed using Top-Down MS and post in-solution digestion gained access to larger proteins via their representative peptides. The UniRef database was used for protein identification searches. Tandem MS data was converted and run through either SEQUEST for Top-Down data, or SEQUEST, X!TANDEM, and MASCOT separately for tryptic peptides. All three of these top matching algorithms were utilized when possible to increase confidence in protein identifications, while also decreasing the propensity for false negatives.

RESULTS Pancreatic juice samples were prospectively collected at operation during August and September 2007. A wide variety of highly scored proteins (553) were identified in the seven usable samples. The Top-Down approach identified 212 cancer-specific and 313 non-cancer related proteins. Only 28 (5.1%) proteins crossed-over between the two groups. Enzyme activity pathways were different between the cancer (ferridase, amylase, pyruvate kinase) and non-cancer (endopeptidase, elastase, lipase, glycosylase, oxidoreductase, limonene oxidase) samples. Small molecule and metal binding pathways (fatty acids, retinol, calcium, copper, steroids, ACE's, actin, etc.) and enzyme inhibitory pathways (peptidases, glycosylases) were specific to cancer samples. Polysaccharide binding and ion transport activity pathways were unique to the non-cancer samples. Specific proteins known to be associated with cancer specific mechanisms (gelsolin, angiotensinogen, profilin, cofilin, calcium binding protein S100, thymosine beta 4, transthyretin, apolipoprotein A-1, and vimentin) were confirmed and different from those observed solely in non-cancer patients (chymotrypsinogen, elastase, trypsin, serine protease, ribonuclease, and carboxypeptidase).

CONCLUSIONS: Combining two separate MS approaches to analyze human pancreatic juice, including that of an automated Top-Down approach developed in our lab, resulted in highly reproducible results. Proteins of both known and novel biomarkers were identified in cancer and non-cancer samples with a much larger number of proteins identified than previously reported. Furthermore, consistently different protein signatures were observed with only a small percentage of cross-over between cancer and non-cancer groups. In general, the protein classes observed in each arm were sharply contrasted; with fatty acid/metal binding proteins and enzyme inhibitors associated with cancer while proteases and polysaccharide binding proteins were associated with non-cancer samples.

Poster #19: **REDUCTION OF LOCAL INFLAMMATORY RESPONSE ON ACUTE PANCREATITIS IN RATS: EFFECTS OF A HYPERTONIC SALINE SOLUTION.**

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Introduction: In acute pancreatitis (AP) local proinflammatory cytokine production within the pancreas may lead to a systemic inflammatory response with potentially fatal multiorgan failure. Previous studies have demonstrated that hypertonic saline solutions present significant potential as an immunomodulator agent. The aim of this study was to evaluate the effect of a hypertonic saline solution on local inflammatory response on acute pancreatitis in rats.

Methods: AP was induced in male Wistar rats by intraductal 2.5% taurocholate injection. The animals were divided in 3 groups: **NT** (n=15): no treated AP, **NS** (n=15): animals received 34ml/kg of normal saline solution (NaCl 0.9%) IV, 1 hour after AP, and **HTS** (n=15): animals received 4ml/Kg of hypertonic saline solution (NaCl 7.5%) IV., 1 hour after AP. After 2 and 24 hours of induction of AP volume of ascitic fluid and TNF-alfa, IL-6 and IL-10 levels in the ascitic fluid and pancreatic tissue were determined by enzyme-linked immunosorbent assay (ELISA). Pancreatic myeloperoxidase (MPO) and malondialdehyde (MDA) were analyzed 2 and 24 hours after AP. Pancreatic histology was also analyzed.

Results: A significant decrease on volume of ascitic fluid and levels of peritoneal TNF-alfa, IL-6 and IL-10 was observed two hours after AP in animals of HTS group ($p < 0.05$). Also, 2 and 24 h after AP a significant reduction on pancreatic levels of TNF-alfa, IL-6 and IL-10 was observed in group HTS when compared to NT and NS groups ($p < 0.05$). However, there were no significant differences in pancreatic MPO, MDA and histological findings (edema, acinar necrosis, hemorrhage, fat necrosis, and inflammation) in animals of the three groups.

Conclusion: These findings suggest that administration of hypertonic saline solution decreases local inflammatory response in acute pancreatitis without changing the intensity of the pancreatic lesions.

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Poster #20: **PREDICTIVE AND PROGNOSTIC VALUE OF CA 19-9 IN RESECTED PANCREATIC ADENOCARCINOMA**

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Background: Although CA 19-9 is most often used in pancreatic cancer as a diagnostic adjunct, or to follow response to treatment, its preoperative value has been reported to correlate with survival and recurrence. A corrected-CA 19-9 (c-CA19-9), obtained by dividing the CA 19-9 by total bilirubin, has been reported to improve this correlation. Our aim is to evaluate the predictive and prognostic value of CA 19-9 in a large single-institutional experience.

Methods: A retrospective review of all patients undergoing pancreatoduodenectomy from July 2001 through June 2007 at our institution was conducted. Preoperative serum CA 19-9 and total bilirubin levels were analyzed with histologic and survival data.

Results: Of 328 patients identified, 231 (58% male; 42% female) with a mean age of 66 (37-90) had both pre-operative serum CA 19-9 and total bilirubin levels and comprised our study group. Median follow-up was 2.1 years. All patients underwent pancreaticoduodenectomy for histologically confirmed pancreatic adenocarcinoma. Using receiver operator curves, neither CA 19-9 nor c-CA 19-9 demonstrated predictive value for lymph node status (c=0.55/0.56) or margin status (c=0.50/0.46). Tumor size and lymph node ratio very weakly correlated with CA 19-9 and c-CA 19-9 levels (Spearman correlation coefficients for tumor size: 0.26 and 0.28; for lymph node ratio: 0.17 and 0.16, respectively). Survival was not different at 1 year (73% vs. 68%), 3-years (33% vs 22%), or 5-years (27% vs 16%) for patients with CA 19-9 \leq 300 compared to those with values $>$ 300. Using corrected c-CA 19-9 with a cut-off of 50 also failed to demonstrate a significant difference in survival. Even at cutoffs of 500 and 100 for CA 19-9 and c-CA-19-9 respectively, there was no difference in survival compared to patients with lower levels ($p>$ 0.2). Patients with a CA 19-9 $>$ 300 or c-CA19-9 $>$ 50 were at 1.30 and 1.29 times risk of death than those with CA 19-9 $<$ 300 or c-CA 19-9 $<$ 50 respectively.

Conclusion: This large, single institution study demonstrates no histologic (lymph node or margin status) predictive value or prognostic value of CA 19-9 or c-CA19-9 in patients undergoing resection for pancreatic adenocarcinoma. These findings are in contrast to smaller previous studies that have suggested such a correlation. Our findings do not support broadening the use of CA 19-9 beyond aiding diagnosis and following therapeutic response.

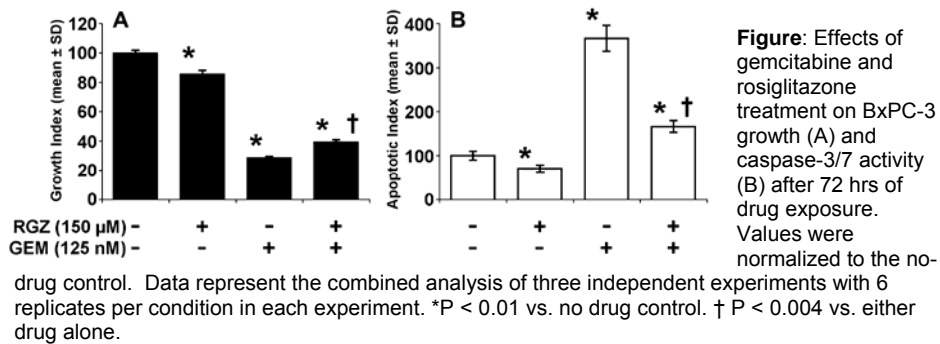
Poster #21: **ROSIGLITAZONE ATTENUATES GEMCITABINE-INDUCED APOPTOSIS VIA CELL-CYCLE INHIBITION IN PANCREATIC ADENOCARCINOMA**

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Introduction: Gemcitabine, the current standard treatment for pancreatic adenocarcinoma (PA), is a nucleotide analog that incorporates into DNA during the S-phase of the cell cycle, thus inhibiting DNA synthesis and inducing apoptosis. However, clinical efficacy is limited by low response rate and acquired resistance. Thiazolidinediones used in the treatment of diabetes, such as rosiglitazone, have also shown promise as potential cancer therapies. In several studies, rosiglitazone inhibited growth and invasiveness of PA cells. We hypothesized that a dual-agent therapeutic strategy involving the delivery of rosiglitazone in combination with gemcitabine would further decrease PA cell growth through synergistic drug action.

Methods: The effects of gemcitabine and rosiglitazone on cell growth and apoptosis were evaluated in several PA cell lines, including BxPC-3 (Figure).
Results: Gemcitabine inhibited BxPC-3 cell growth ($EC_{50} = 8 \pm 2 \text{ nM}$) and induced apoptosis, as measured by caspase-3/7 activity. Rosiglitazone alone showed modest growth inhibition ($EC_{50} = 256 \pm 24 \text{ }\mu\text{M}$) and did not induce apoptosis, but instead decreased caspase activity. Unexpectedly, dual drug treatment resulted in an antagonistic interaction, with a reduction in both gemcitabine-induced growth inhibition and apoptosis. We considered that the antagonistic interaction might result from rosiglitazone-induced cell-cycle arrest preventing progression to S-phase, which is required for gemcitabine incorporation and activity. We examined the effect of rosiglitazone and gemcitabine on G1/S cell cycle regulators. In BxPC-3, rosiglitazone increased expression of p21 and decreased phosphorylation of Rb, suggesting a reduction in progression to S-phase.

Conclusions: Rosiglitazone-dependent G1/S cell cycle arrest could explain the antagonism between the two drugs. These data indicate that, under some situations, rosiglitazone may interfere with gemcitabine therapy of PA, and care should be taken in treating patients on anti-diabetic drugs.



Poster #22: **CENTRAL PANCREATECTOMY PRESERVES PANCREATIC ENDOCRINE FUNCTION**

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Introduction: The potential benefits of limited pancreatic resection with central pancreatectomy include spleen conservation and putative long-term preservation of endocrine/exocrine pancreatic function without oncologic compromise. Critics of central pancreatectomy cite the associated morbidity of pancreatic fistula, ranging from 13-63%. To examine this question we compared the incidence of pancreatic fistula and the incidence of endocrine and exocrine insufficiency in patients who underwent central pancreatectomy versus patients who underwent distal pancreatectomy.

Methods: A retrospective review of a prospectively maintained database identified patients who underwent central pancreatectomy (n = 17) or distal pancreatectomy/splenectomy (n = 93) for primary lesions of the pancreas between 1994 and 2007. Clinicopathologic data from both patient groups were analyzed, with particular attention paid to postoperative pancreatic fistula, long-term endocrine/exocrine function and oncologic outcome.

Results: Indications for central pancreatectomy (CP) included PNET (n=7), IPMN (n=5), solid pseudopapillary neoplasm (n=3), papillary epithelial neoplasm (n=1), and adenosquamous carcinoma (n=1). Indications for distal pancreatectomy/splenectomy (DP) included PNET (n= 37), mucinous cystic tumors (n=26), IPMN (n=5), serous cystadenoma (n=10), solid pseudopapillary (n=6), and other (n=9). Median follow-up times for central and distal pancreatectomy were 9.7 and 28.5 months, respectively. The incidence of pancreatic fistulae in patients who underwent CP was 47.1% compared to 18.3% in the DP group (p=.052). All fistulae were controlled by either intraoperative or percutaneous drain placement. Postoperative exocrine insufficiency requiring long-term use of pancreatic enzyme replacement therapy for CP and DP was 29.4% and 7.5%, respectively (p=.039). Postoperative endocrine insufficiency requiring insulin and/or oral hypoglycemic agents was 6% in patients who underwent CP compared to 29% in the DP group (p=.0013).

Conclusion: Central pancreatectomy permits successful oncologic resection of pancreatic neoplasms in appropriately selected patients. CP may confer higher rates of pancreatic fistulae and can be managed by percutaneous drainage with minimal morbidity. Central pancreatectomy may also result in higher rates of exocrine insufficiency, which can be managed by oral pancreatic enzyme supplementation. Most importantly, CP results in significantly less endocrine insufficiency with decreased postoperative use of oral hypoglycemics and insulin which may affect long term patient health.

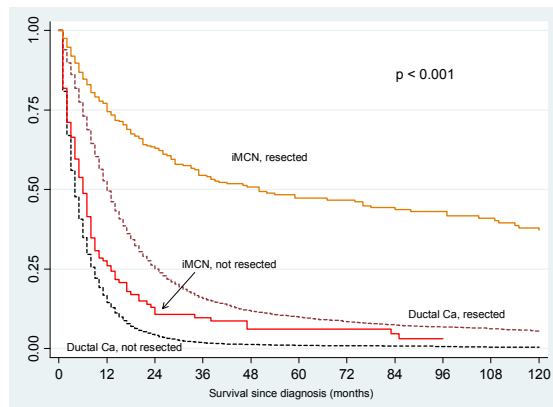
Poster #23: **POPULATIONAL CHARACTERISTICS AND OUTCOMES OF 661 MUCINOUS CYSTIC CARCINOMAS OF THE PANCREAS.**

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Background: Mucin-producing cystic lesions of the pancreas have malignant potential, but the natural history of these lesions remains poorly understood. Based upon the available literature, clinical management algorithms have been developed that rely upon a variety of features. A populational analysis of these cancers has not been reported. Therefore, we performed a populational analysis of characteristics and outcomes of mucin-producing cystic cancers of the pancreas.

Methods: The Surveillance, Epidemiology, and End Results data from 1973 through 2004 were analyzed for incidence, features and outcomes of mucin-producing cystic carcinomas of the pancreas with clear evidence of invasive properties (iMCN).

Results: Review of 661 iMCNs revealed the incidence of iMCNs increased early in the study period, but stabilized in the last five years to 0.67 cases per million. Invasive MCNs present at younger age (66 ± 15 versus 68 ± 13 years, $p < 0.001$), earlier stage (metastases in 22% versus 52%,



$p < 0.001$), and are more often resected (54% versus 15%, $p < 0.001$) as compared to pancreatic ductal carcinoma. Median survival is 7.5 months for pancreatic ductal adenocarcinoma versus 15.3 months for iMCNs ($p < 0.001$). Age, gender, tumor size and grade do not reliably predict nodal ($p = 0.381$) or systemic ($p = 0.126$) metastases. Significant predictors of better survival in a multivariable model were IPMN histology (HR=0.483, $p = 0.038$), resection (HR=0.629, $p = 0.036$), lower stage (HR=1.929, $p < 0.001$) and younger age (HR=1.028, $p < 0.001$).

Conclusions: Invasive MCNs are uncommon and are not increasing in incidence. Early stage lesions carry a better prognosis as compared to pancreatic ductal carcinoma, while IPMNs with invasive biology have an even better prognosis than mucinous cystadenocarcinomas. Age and lesion size criteria miss a substantial proportion of patients with invasive malignancy.

Poster #24: **RETROSPECTIVE VALIDATION OF INTERNATIONAL CONSENSUS GUIDELINES FOR MANAGEMENT OF BRANCH DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (BD-IPMN)**

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Background: The risk of branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) for prevalent or incident malignancy is thought to be low. Hence, a working group of The International Association of Pancreatology (IAP) has proposed guidelines for the management of BD-IPMNs (Tanaka et al, Pancreatology 2006). Resection is recommended for all patients with symptomatic IPMNs and suspected main duct IPMNs who are surgical candidates. Resection is not recommended if an asymptomatic BD - IPMN is < 3 cm in size, if there are no high risk stigmata (main pancreatic duct dilation > 6 mm, mural nodules), or is without malignant cytology.

AIM: To apply IAP consensus guidelines to a large cohort of patients with resected BD-IPMNs to determine (1) the proportion of potentially missed malignancies and the (2) the frequency of surgery for asymptomatic non-malignant BD-IPMNs, assuming the targets for resection were IPMN with carcinoma-in-situ (CIS) or invasive cancer (CA).

METHODS: Prospective EUS and pathology databases were queried for IPMNs that were evaluated and/or treated at Johns Hopkins Hospital from 1990-2006. Main duct IPMNs without a cyst were excluded. Positive cytology was defined as mucinous pancreatic ductal epithelium definitive or suspicious for malignancy. Univariate and bivariate categorical analysis on the prevalence of malignancy (as CIS or invasive CA) was performed.

RESULTS: 132 patients (52% men, 86% white, mean age=67 years) with at least 1 BD-IPMN underwent surgery from 1990-2006. 44 patients (33%) also had EUS in addition to multidetector CT and all but 1 had EUS-guided FNA. Mural nodules were detected in 10 (22.7%) and positive cytology obtained in 6 patients (13.9%). Forty-five percent (59/132) of BD-IPMNs had CIS (n=23) or CA (n=36) and 24% of these had no associated symptoms. According to consensus guidelines, 24/59 (41%) malignant BD-IPMNs would not have been resected if surgery was performed only on BD-IPMNs > 3 cm. In 48 patients without symptoms, surgery was performed on 10 (21%) without malignancy (IPMN-adenoma/-borderline) due to size of the neoplasm.

CONCLUSIONS: When applied to a highly selected single center referral population, current consensus guidelines on the management of BD-IPMNs would not recommend surgery in 41% of malignant BD-IPMNs and recommend unnecessary surgery in 10%. Adherence to IAP guideline recommendations may lead to suboptimal management of BD-IPMNs. Development and validation of a better model for prediction of prevalent malignancies in BD-IPMNs are needed.

Poster #25: **PREOPERATIVE CA19-9 IN THE NEOADJUVANT TREATMENT OF RESECTABLE PANCREATIC CANCER**

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Introduction/Background: Gemcitabine-based preoperative chemoradiation for patients with potentially resectable adenocarcinoma of the pancreatic head was studied in two recently completed clinical trials at our institution (in press: *J Clin Oncol*). Those reports do not contain an analysis of serum levels of carbohydrate antigen (CA) 19-9 which is the subject of this report.

Methods: Neoadjuvant gemcitabine-based chemoradiation was delivered to 176 patients with biopsy proven pancreatic adenocarcinoma between 1998 through 2006. All patients were determined to have potentially resectable disease based on defined CT imaging criteria. The protocols did not mandate measurement of serum level of CA 19-9, however, this data was available in most patients. CA19-9 levels which were unmeasurable (indicative of individuals with the Lewis a-b- blood group antigen who do not synthesize CA19-9) and those associated with an elevated serum bilirubin (> 1.5 mg/dL) were excluded from analysis. Endpoints of analysis included the completion of all therapy to include pancreaticoduodenectomy (PD), histologic response in the resected specimen, and survival duration.

Results: Pretreatment CA19-9 levels were evaluable in 96 patients (median 153 U/mL, range 2–8614 U/mL) and post-treatment (preoperative) CA 19-9 levels were available in 128 patients (median 44 U/mL, range 1–6927 U/mL). Median survival for the entire cohort was 19.8 months. There was no significant difference between the median survival of patients who did and did not have evaluable pretreatment CA19-9 levels. The maximum pretreatment CA 19-9 level in patients who underwent PD and remain disease free was 1125 U/mL. The maximum preoperative CA 19-9 level in patients who underwent PD and remain disease free was 934 U/mL. Both pretreatment and preoperative CA 19-9 levels were available in 81 patients. When comparing the pretreatment to the preoperative CA19-9 levels, a decrease of > 50% occurred in 49 (60%) and a decrease of < 50% occurred in 13 (16%) patients. The CA 19-9 rose or remained the same in 19 (23%) patients. The percentage change in serum CA19-9 from pretreatment to preop did not predict resectability or survival after resection among patients who underwent PD. There was no correlation between the change in CA19-9 and histologic score of treatment effect.

Conclusion/Discussion: These data suggest that the absolute value of CA19-9 and its change from pretreatment to preop can not accurately predict outcome in a homogenous population of patients with stage I/II adenocarcinoma of the pancreatic head. This may not be the case for patients whose staging evaluation is not as detailed or those with borderline (or more advanced) disease. Due to relatively small numbers, these results will need confirmation in a larger population of patients who are equally well defined in terms of performance status and extent of disease.

Poster #26: **SURGICAL RESECTION OF METASTATIC RENAL CELL CARCINOMA TO THE PANCREAS**

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Background: Metastatic lesions to the pancreas account for less than 2% of pancreatic neoplasms. Outcomes of pancreatic resection for disease-specific metastases are poorly defined due to their low incidence and grouping of multiple tumor types in current series. Renal cell carcinoma appears to be the most common source of pancreatic metastases. Overall 5-year survival rates for unresected metastatic renal cell carcinoma are typically less than 10%. Our aim is to define the surgical management and outcome of patients with metastatic renal cell carcinoma to the pancreas.

Methods: Retrospective review of all patients who underwent pancreatic resection for metastatic renal cell carcinoma at our institution from January 1990 to November 2007. Analysis included clinical evaluation, operative management, histology, and outcomes.

Results: A total of 32 patients (18 male, 14 female) with a mean age of 68 years (44-82) were identified. Presentation of the pancreatic metastases was metachronous in 31 patients and synchronous in 1. Solitary pancreatic metastases were identified in 21, while 11 patients had multiple pancreatic metastases (range: 1-6). Resection was limited to the pancreas (n=19), involved additional metastatic sites (n=9), or included renal-bed recurrence (n=3). The median interval from nephrectomy to pancreatic resection was 9 years (1-42). Pancreatic resection included distal pancreatectomy (n=26), total pancreatectomy (n=3), and pancreaticoduodenectomy (n=2). R0 resection was accomplished in 31 patients (97%). One patient underwent a palliative (R2) resection. One patient underwent completion pancreatectomy for recurrent pancreatic metastases 55 months after distal pancreatectomy. Perioperative mortality was not observed. Follow-up data was available in 31 patients (97%) for a mean of 53 months. Tumor recurrence was observed in 15 patients (48%), a mean of 29 months (4-96) after pancreatic resection. Disease-free and overall survival following pancreatic resection was 35 and 53 months respectively, with an actual 5-year survival of 42%.

Conclusion: Metastatic renal cell carcinoma is typically associated with poor survival. Pancreatic resection for metastases may offer a survival advantage; however, potential patient selection bias and lack of comparative trials limit validation. Pancreatic resection does appear warranted in selected patients where an R0 resection is possible.

Poster #27: **K-RAS DIRECTS LIGAND-DEPENDENT CXCR4 SIGNALING IN PANCREATIC CANCER AND REGULATES PROLIFERATION THROUGH THE MITOGEN ACTIVATED PROTEIN KINASE PATHWAY**

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Background:

K-ras mutation, which results in constitutive K-Ras activity, has been theorized to have a central role in the pathogenesis of pancreatic cancer. Recently, chemokine receptor CXCR4 has been implicated in the invasive phenotype of pancreatic cancer. Although CXCR4 distributes its downstream signals through various signaling mediators, it is unclear whether mutant K-ras conducts or amplifies CXCR4 signaling. We hypothesized that K-ras and CXCR4 cooperate to enhance pancreatic cancer proliferation.

Methods:

We evaluated pancreatic cancer cells PANC-1 and BxPC-3 with mutant and wild-type K-ras alleles, respectively. RNA interference was used to knockdown K-ras in order to measure its contribution to CXCR4-mediated proliferation. The downstream effectors AKT and ERK-1/2 were assessed to determine their roles in CXCR4-mediated proliferation.

Results:

We found in both cell lines that exposure to CXCL12, the specific CXCR4 ligand, increased phosphorylation of ERK-1/2 (pERK-1/2); phosphorylation of AKT (pAKT) was only increased in PANC-1 cells. This increase in pERK-1/2 correlated with enhanced proliferation in PANC-1 cells. With K-ras knockdown in PANC-1 cells, levels of pAKT and pERK-1/2 and subsequent proliferation decreased. MEK/ERK-1/2 blockade abrogated CXCR4-mediated proliferation, whereas PI-3K/AKT blockade increased the phosphorylation of ERK-1/2 and increased proliferation.

Conclusions:

In summary, our studies show that CXCR4 signaling is mediated by mutant or wild-type K-ras through AKT or ERK-1/2 and subsequent increases in CXCR4-mediated proliferation are specifically propagated through ERK-1/2.

Poster #28: **COX-2 OVEREXPRESSION CONFERS SURVIVAL TO PANCREATIC CANCER CELLS**

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Background and Aim: There is substantial evidence that cyclooxygenase-2 (COX-2), the rate-limiting enzyme for prostanoid production, significantly contributes to the phenotype of human malignancies. Targeting the COX-2/prostanoid pathway is considered an intriguing approach for therapy and prevention of several human cancers. We have previously demonstrated that selective COX-2 inhibitors attenuates the growth of human pancreatic cancer (PaCa) in a xenograft mouse model and delays the progression of PaCa precursor lesions in a genetically engineered mouse model. However, the precise molecular signals that underlie the pro-tumorigenic properties of COX-2 in PaCa are still poorly described. The aim of the present study therefore was to characterize the phenotype of COX-2 expressing human PaCa cells.

Methods and Results: The undifferentiated human PaCa cell line MIA PaCa-2, which lacks COX-2 expression, was stably transduced with a third generation lentiviral construct harboring the full length human COX-2 cDNA and GFP as a marker. Lentiviruses encoding only for GFP were used as a control. Transduced MIA PaCa-2 cells were sorted to yield $\geq 95\%$ pure cell populations (MP2^{-COX2} and MP2^{+COX2}). Western blot and immunofluorescence confirmed successful and stable COX-2 expression. Adding the COX-2 substrate arachidonic acid (AA, 10 μ M) to the cell cultures for 1-24 hours lead to a marked time-dependent increase in PGE₂ production in MP2^{+COX2} cells (13-fold, 9-fold, and 3-fold increase after 1, 3, and 6 hours, respectively, compared to MP2^{-COX2}). Anchorage-dependent growth assays (cell count, MTT) demonstrated an increase in cell growth in MP2^{+COX2} compared to MP2^{-COX2} cells in the presence of AA (110% increase after 6 days). Using a Human Apoptosis PCR Array comprising of 84 different cell death-related genes, significant differences (>2 fold increase or decrease in gene expression) were detected between MP2^{+COX2} and MP2^{-COX2} cells in several genes, including members of the bcl-2 family, caspase family, and TNF receptor superfamily.

Conclusions: We have established a model to delineate the contributions of COX-2 to the malignant phenotype of human pancreatic cancer cells. Stable overexpression of COX-2 in pancreatic cancer cells leads to an elevated production of prostanoids and increased cell growth. In addition, expression of COX-2 was associated with a differential expression of several cell-death related genes. These findings will provide the basis for more mechanistic studies on the role of COX-2 in pancreatic cancer and may help to develop novel therapeutic strategies in pancreatic cancers aiming at the COX-2/prostanoid pathway.

Poster #29: **THE STRIKING INCIDENCE OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED PATIENTS WITH NECROTIZING PANCREATITIS**

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Background: Acute pancreatitis is a substantial medical problem, accounting for more than 220,000 hospital admissions yearly in the US. Twenty percent of these patients will develop necrotizing pancreatitis (NP), which is characterized by pancreatic and peripancreatic necrosis. Venous thromboembolism (VTE) is also a major national health concern, with an incidence in all hospitalized patients approaching 10%. Surprisingly few data are available regarding VTE in NP. The aim of this study was to determine the incidence of VTE in patients with NP.

Methods: Retrospective review (1992-2007) of patients with NP treated at a University Hospital. The diagnosis of VTE was confirmed using standard radiographic criteria for duplex ultrasonography (U/S) or helical Computed Tomography (CT). Chi square was used to compare discrete variables, accepting $p < 0.05$ as statistically significant.

Results: 171 patients with NP were identified. Of these, 96 patients (56%) had radiographic evidence of VTE. Fifty-one (53%) of patients VTE had thrombi identified in multiple locations for a total of 152 DVT identified in this series. Four patients (2%) had documented pulmonary emboli. DVT was found more frequently in abdominal vasculature (121/78%) as compared to the extremities (31/20%) ($p < 0.001$). Fourteen out of sixteen (88%) patients with an upper extremity DVT had an associated intravenous catheter. The following table details DVT location.

Table

Location	Splenic	SMV/PV	LE	UE	Catheter Associated	PE
# (%)	63(40)	58(37)	15(10)	16(10)	14 (88*)	4(2)

SMV/PV – superior mesenteric/portal vein, UE- upper extremity, LE- lower extremity, PE – pulmonary embolus

*88% of UE DVT were associated with an intravenous catheter.

Conclusion: These data demonstrate that: 1) 56% of patients with NP have associated DVT and that 53% of these patients had more than one thrombus, 2) Patients with NP are more likely to develop abdominal DVT (78%) compared to extremity DVT (20%), and 3) 88% of UE DVT are associated with catheter placement. From these data, we conclude that VTE is a significant problem in patients with NP and that aggressive VTE prophylaxis should be implemented.

Poster #30: **LONG-TERM OUTCOME AFTER 92 DUODENUM-PRESERVING PANCREATIC HEAD RESECTIONS FOR CHRONIC PANCREATITIS: COMPARISON OF FREY- AND BEGER-PROCEDURES**

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Introduction: Duodenum-preserving pancreatic head resections (DPPHR) in the techniques described by FREY or BEGER may be an alternative to pancreaticoduodenectomy (PD) or drainage procedures for chronic pancreatitis (CP) predominantly of the pancreatic head. Data comparing the outcomes after both operations are rare. We, therefore, analyzed our long-term results after DPPHR in 92 patients.

Methods: Since 1995 113 patients underwent DPPHR for CP predominantly of the pancreatic head. The decision to perform either a FREY- or a BEGER procedure was always made individually depending upon the complications and morphological classification of CP. Up to now prospective outcome results including standardized questionnaires could be obtained in 92 patients with a median postoperative follow-up of 43 months. Of those 92 patients (82% male, median age 44 years) 77% had alcoholic CP. The leading indications for surgery were pain (87%), recurrent attacks of CP (90%), jaundice (22%) or symptomatic duodenal stenosis (10%).

Results: Any / surgery related postoperative complications occurred in 31%/20% after FREY-procedures and in 41%/30% after BEGER-procedures (n. s.). In median 43 months after surgery 62% (FREY) and 50% (BEGER) of the patients were completely free of pain, respectively. In the collection of patients still or again suffering from pain (FREY vs. BEGER) 6% / 19% had pain at least once per week or daily and the remaining 32% / 31% experienced pain attacks at least once per year (difference for pain frequency $p=0.55$).

Diabetes was documented in 57% (BEGER) and 60% (FREY; n.s.). During postoperative follow-up a de-novo diabetes occurred in 17% after BEGER- and in 34% after FREY-procedures ($p=0.06$). The frequencies of an exocrine insufficiency (74% vs. 76%, $p=0.8$) and a postoperative de-novo exocrine insufficiency (33% vs. 34%; $p=0.9$) were identical. The median gain in body weight until the last follow-up was not significantly different (three kg after BEGER vs. two kg after FREY). Two patients in each group had relevant biliary complications (stenosis or symptomatic duct stones) during follow-up requiring re-intervention. Actuarial five-year survival after DPPHR was 96% and clearly higher than survival in the 110 patients who underwent PD for CP at our institution (five-year survival 82%).

Conclusions: Comparison of the outcomes after either a FREY- or a BEGER-procedure for CP reveals a tendency for better pain control after the FREY-operation. The functional outcomes (organ function, biliary) were almost identical. Surprisingly, late mortality after DPPHR was clearly lower than reported in other series and in the patients undergoing PD for CP at our institution.

Poster #31: **THE LYMPH NODE-RATIO IS THE STRONGEST FACTOR PREDICTING SURVIVAL AFTER RESECTION OF PANCREATIC CANCER.**

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Survival after surgery of pancreatic cancer is still poor even after curative resection. Some prognostic factors like the status of the resection margin, lymph node (LN) status or tumor grading were identified. However, only few data have been published regarding the prognostic influence of the LN-ratio (number of LN involved to number of examined LN), with sometimes conflicting results. We, therefore, evaluated potential prognostic factors in 182 patients after resection of pancreatic cancer.

Methods: Since 1994 204 patients underwent pancreatic resection for ductal pancreatic adenocarcinoma. Survival was evaluated in 182 patients with complete follow-up evaluations (54% female). Of those 182 patients 88% had cancer of the pancreatic head, 5% of the body and 7% of the pancreatic tail. Patients underwent pancreatoduodenectomy (86%), distal resection (11%) or pancreatectomy (3%). Survival was analyzed by the Kaplan-Meier- and Cox-methods.

Results: In all 204 resected patients mortality was 3.9% (n=8). In the 182 patients with follow-up 70% had free resection margins, 62% had G1 or G2-classified tumors and 70% positive LN. Median tumor size was 30 (7-80) mm. The median number of examined LN was 16, median number of involved LN one (range 0-22). Median LN-ratio was 0.1 (0-0.79). Cumulative five-year survival (5-y SV) in all patients was 16%. In univariate analysis a LN-ratio ≥ 0.2 (5-y SV 6% vs. 19% with LN-ratio < 0.2 ; $p=0.003$), LN-ratio ≥ 0.3 (5-y SV zero% vs. 18% with LN-ratio < 0.3 ; $p<0.001$), a positive resection margin ($p<0.01$) and poor differentiation (G3/G4; $p<0.03$) were associated with poorer survival. In multivariate analyses a LN-ratio ≥ 0.2 ($p<0.01$; relative risk RR 1.7) or a LN-ratio ≥ 0.3 ($p<0.001$; relative risk RR 2.4), positive margins ($p<0.03$; RR 1.6) and poor differentiation ($p<0.05$; RR 1.4) were independent factors predicting poorer outcome. The LN-ratio as a continuous variable also significantly correlated with survival whereas the conventional nodal status or the number of involved LN per se had no significant influence on survival. Patients with one LN involved had the same outcome than patients with negative nodes but prognosis worsened significantly in patients with two or more LN involved.

Conclusions: Not the lymph node involvement per se but especially the LN-ratio is an independent prognostic factor after resection of pancreatic head cancers. In our series this LN-ratio was even the strongest predictor of survival (cutoff ~ 0.2). The routine estimation of this LN-ratio may be helpful not only for the individual prediction of prognosis but also in the planning of adjuvant therapy and further outcome and therapy studies.

Poster #32: **HIGH- AND LOW-PASSAGE VARIANTS OF A HUMAN PANCREATIC CANCER CELL LINE YIELD TWO DIFFERENT IN VIVO MODELS OF PANCREATIC CANCER PROGRESSION**

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Introduction/Background:

Despite its relatively low incidence in the population pancreatic cancer remains the fourth leading cause of cancer-related death in the United States. The lethality of this disease is due to both its late presentation and the lack of effective systemic therapies. Preclinical in vivo evaluations of antitumor therapies predominantly rely on murine model systems, which can often be time-consuming and variable.

Methods:

The human pancreatic cancer cell line XPA-1 was stably transduced to express red fluorescent protein (RFP) and was implanted into the pancreas of the nude mouse. Malignant ascites from these animals were serially passaged into the pancreas of nude mice through 6 generations to develop P6 ascites XPA-1 RFP cells. Animals were followed using whole body imaging using the Olympus OV-100 Small Animal Imaging System and evaluated by necropsy at the time of death. Tumor tissue from these animals was evaluated by histology and used to generate cell lines which were tested for differences in cell proliferation in vitro.

Results:

In the P0 generation the XPA1-RFP tumors grew slowly with eventual metastasis to multiple extrapancreatic sites including diaphragm, lung, abdominal lymph nodes, liver, spleen and mesentery by weeks 9-12 after implantation. Repeated passage of the ascites cells into the pancreas of nude mice yielded a much more rapid growth of primary tumor as well as a shorter time to metastasis. In the P6 generation lesions were seen in the liver, spleen, abdominal lymph nodes, mesentery and lung by 3-5 weeks after implantation. Time to death in the P0 generation was from 12-14 weeks while the P6 generation was from 3-7 weeks. The sites of metastasis did not differ between the P0 and P6 generation, and H&E evaluation of the primary and metastatic tumor revealed lesions that appeared histologically similar. In vitro testing of cell proliferation yielded no significant difference between the original XPA-1 RFP cell line and P6 ascites XPA-1 RFP cell lines derived from either malignant ascites or primary pancreatic tumor tissue.

Discussion/Conclusion:

Selection of a high-passage variant of the human pancreatic cancer cell line XPA1-RFP (P6 ascites XPA1-RFP) yielded a population of cells with highly aggressive in vivo growth and metastasis without demonstrable increase in vitro cell proliferation. The P0 and P6 generation XPA-1 RFP cell lines provide models which can facilitate the testing of therapeutics targeting to early and late events in tumor growth and metastasis. The slower-growing P0 generation tumor model allows for testing of anticancer agents designed to prevent growth of the primary tumor, while the P6 generation facilitates the evaluation of agents designed to impair tumor invasion and metastasis. These two models offer multiple applications for the testing of pancreatic cancer therapeutics in the nude mouse.

Poster #33: **THE ROLE OF PANCREATIC SPHINCTEROPLASTY FOLLOWING ROUX-EN-Y GASTRIC BYPASS**

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INTRODUCTION: Patients who have undergone Roux-en-y gastric bypass (GB) for morbid obesity frequently develop post-operative abdominal pain disorders which require surgical evaluation. Chronic pancreatitis and pain associated with Sphincter of Oddi Dysfunction (SOD) and Pancreas Divisum (PD) are uncommon disorders, and thus diagnosis in the GB population is problematic. In order to evaluate the diagnosis and treatment of SOD and PD in the GB population, a retrospective review and analysis of GB patients who underwent transduodenal sphincteroplasty (TS) for SOD and PD was undertaken.

METHODS: The medical records of patients who underwent TS post GB at the Medical University of South Carolina Digestive Disease Center between January 2001 and December 2005 were evaluated for outcomes based data with the approval of the Institutional Review Board for the evaluation of human subjects. Long term patient outcomes were assessed by a standardized patient satisfaction questionnaire and the SF-36 version 2 Quality of Life Survey.

RESULTS: Twelve women (mean age 45) were identified. Ten patients with SOD underwent TS with biliary sphincteroplasty and pancreatic ductal septoplasty; two patients with PD underwent minor duct septoplasty. Indications for surgery included pain (100%), nausea (25%), weight loss (8.3%), and recurrent pancreatitis (25%). Diagnosis of SOD and PD was supported by magnetic resonance cholangiopancreatography (MRCP) with secretin stimulation. There was one post-operative complication (8%) and no mortality. The average length of hospital stay was 5 days (range 2 to 9 days). Eight out of 12 (66%) patients responded to survey follow-up. Mean length of follow-up was 31 months (range 16 to 57 months). Seven out of 8 (87.5%) patients reported pain improvement following operation. The SF-36 version 2 Quality of Life norm based scores were similar to a representative population.

CONCLUSIONS: SOD and PD should be considered in the differential diagnosis of GB patients with pancreato-biliary pain postcholecystectomy. When the clinical history is supported by laboratory and MRCP data, TS can be undertaken with low morbidity and good patient outcome. SOD and PD are notable disorders in the GB population. With appropriate patient selection, TS can be beneficial.

Poster #34: **DISTAL PANCREATECTOMY IN THE MODERN ERA: EVOLUTION OF A PROCEDURE**

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INTRODUCTION: By the 1990s, distal pancreatectomy had become a safe operation at high-volume centers. In recent years the increased detection of "pancreatic incidentilomas" and the emergence of laparoscopic resection have altered the indications. However, the indications for and impact of the laparoscopic approach on a population of patients requiring distal pancreatectomy have not been reported. Therefore, the aim of this analysis was to document how the outcomes of distal pancreatectomy have changed in the modern era.

METHODS: All distal pancreatectomies performed at a single institution from 1995 through 2007 were analyzed. Patient data from operations performed before January, 2004 (n=140) and since (n=214) were documented. During the past four years, 68 operations (31%) were performed laparoscopically.

RESULTS: In comparing patients before and after 2004, no differences were observed in age, gender or BMI, but fewer recent patients had adenocarcinomas (8 vs 19%, p<0.05). Since 2004, patients undergoing laparoscopic (Lap) distal pancreatectomy were more likely to have cystic tumors (46 vs 18 %, p<0.001) and less likely to have pancreatitis (21 vs 50%, p<0.01). Operative (OP) and postoperative outcomes are presented in the Table.

	N	Splenic Preservation	OP Time (min)	EBL (ml)	LOS (days)	Morbidity	Mortality
1995-03 Open	140	7%	183	1469	9.1	39%	1.4%
2004-07 Open	146	16%*	240*	1227	12.4*	60%*	2.1%
2004-07 Lap	68	47%*†	277*	523*†	6.0*†	41%†	1.5%

* p<0.05 vs 1995-03 Open, † p<0.01 vs 2004-07 Open

CONCLUSIONS: This analysis suggests that 1) the indications for distal pancreatectomy have changed, 2) patients undergoing distal pancreatectomy laparoscopically have improved outcomes, and 3) in current patients requiring open surgery the operation is more difficult and the morbidity is increased. We conclude that laparoscopic distal pancreatectomy should be performed in carefully selected patients by surgeons with expertise in laparoscopic and pancreatic surgery.

Poster #35: **THE EFFECT OF AGE ON SHORT-TERM OUTCOMES AFTER PANCREATIC RESECTION: A POPULATION-BASED STUDY**

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Introduction: Pancreatic cancer is a disease of the elderly. Data from single-institution studies have evaluated outcomes following pancreatic resection in elderly patients, but it is unclear if these findings hold true in the general population. The goal of this study is to evaluate a large population-based cohort to determine age-dependent short-term outcomes following pancreatic resection.

Methods: We identified all pancreatic resections in Texas from 1999-2005. Patients were stratified into four age groups (<60, 60-69, 70-79, and 80+ years). Bivariate and multivariate analyses were performed to determine the effect of age on mortality and discharge to a skilled nursing facility (SNF).

Results: 3,736 patients underwent pancreatic resection. Results by age group are shown in the table. Mortality was higher in older patients and they were more likely to require a SNF at discharge. Low-volume (LV) hospitals (<11/year) had higher mortality rates, but the difference in mortality between high (HV) and LV hospitals was more striking in older patients. With increasing age group, mortality increased from 3.0% to 9.5% to 11.4% to 14.5% at LV hospitals. It increased from 2.0% to 3.5% to 4.5% to 8.7% at HV hospitals. In the multivariate model, older age group independently predicted increased mortality. The OR for patients 70-79 was 1.8 (P=0.02) and the OR for patients 80+ was 4.3 (P<0.0001) when compared to patients <60.

	<60 years (n=1780)	60-69 years (N=887)	70-79 years (N=855)	80+ years (N=214)	P-value
Female	54%	49%	49%	55%	0.04
Caucasian	57%	66%	70%	74%	<0.0001
Periampullary Cancer	44%	68%	72%	74%	<0.0001
Resected at HV hospital	62%	62%	57%	54%	0.01
Mortality	2.4%	5.8%	7.4%	11.4%	<0.0001
Discharge to SNF	17%	23%	39%	51%	<0.0001
Length of stay (median)	11 days	13 days	14 days	15 days	0.02

Conclusions: Contrary to previous single-institution studies, increased age is an independent risk factor for mortality following pancreatic resection. For all ages, mortality rates were higher at LV hospitals, but the difference worsened with increasing age. Older patients are more likely to require discharge to a SNF.

Poster #36: **SURVIVAL AFTER PANCREATICODUODENECTOMY IS NOT IMPROVED BY EXTENDING RESECTIONS TO ACHIEVE NEGATIVE MARGINS**

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INTRODUCTION: Resection remains the only hope of cure for pancreatic adenocarcinoma. Microscopically positive margins of resection negatively impact survival. This study was undertaken to determine the survival benefit, if any, of extending resections to obtain microscopically negative pancreatic margins after initial positive intraoperative frozen sections.

METHODS: Since 1995, patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma are followed prospectively. Margin status has been codified as micro- / macroscopically negative (R0) or microscopically positive / macroscopically negative (R1). After resection, stage has been assigned using AJCC guidelines, 6th edition. The impact of margin status on survival was evaluated on a cross-section of patients utilizing survival curve analysis (Log-rank test).

RESULTS: Of 179 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma, complete tumor extirpation (R0) was initially achieved in 134 patients, was ultimately achieved in 17 patients who required extended pancreatic resections after initially positive intra-operative frozen sections (R1→R0), and not achieved in 28 patients (R1). No correlation between AJCC Stage and margin status was identified by regression analysis. Patients undergoing R0 resections lived longer than patients undergoing R1 resections (Table). Survival was not improved if the pancreatic resections were extended to obtain negative (R1→R0) margins (Table).

Resection	Number of Pts.	Median Survival	p-value Relative to R1 Resections
R0	134	21 months	p=0.009
R1→R0	17	11 months	p=0.343
R1	28	13 months	N/A

CONCLUSION: Although resection remains the only hope for cure for patients with pancreatic cancer, even with resection survival is disappointing. Patients undergoing less than complete tumor extirpation have particularly poor survival. Survival after pancreaticoduodenectomy is not improved by extending resections to achieve negative pancreatic margins after initial positive intraoperative frozen sections, suggesting the importance of “tumor specific” factors (e.g., tumor size, infiltrating nature, tumor immunobiology, ...) relative to margin status.

Poster #37: IS ADJUVANT THERAPY INDICATED AFTER PANCREATECTOMY FOR ADENOCARCINOMA?

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Introduction Resection is the only hope of cure for patients with pancreatic cancer, though 5-year survival after resection remains dismal. With hope of improving survival, application of adjuvant therapy is intuitively rational. However, adjuvant therapy is applied to a minority of patients after pancreatectomy. The rationale of adjuvant therapy is disconnected from its application. This study was undertaken to assess the data supporting adjuvant therapy following pancreatectomy for adenocarcinoma.

Methods The National Library of Medicine and the National Institutes of Health were searched for trials of adjuvant therapy after pancreatectomy for adenocarcinoma published since 1980. This search identified 191 trials; 10 were observation-controlled prospective randomized trials. Each trial was graded on its level of data utilizing a National Cancer Institute scale (best score of 1iA to worst score of 3iiidiii). Methodological deficiencies, including inclusion of other cancers, excluded 7 trials from further review. Meta-analysis was applied to 3 observation-controlled prospective randomized trials of adjuvant therapy. Data collected from the trials included therapies utilized, median survival, 1-year, 2-year, and 5-year survival, and differences in survival by survival curve analysis (Table).

Results

Author	Therapy	Grade	# Patients	Median Survival (months)	1-year Survival	2-year Survival	5-year Survival	Survival Curve Difference
GITSG	5FU/XBRT→5FU	1iiA	21	20	63%	42%	19%	p=.03
	observation		22	11	49%	15%	8%	
Klinkenbijl	5 FU/XBRT	1iiA	60	17.1	68%	37%	20%	p=.10
	observation		54	12.6	54%	23%	10%	
Oettle	Gemcitabine	1iiD	179	22.1	72.5%	48%	23%	p=.06
	observation		175	20.2	72.5%	42%	12%	

Meta-analysis attests that there was not a significant advantage to adjuvant therapy during the first two years after resection, but that a survival advantage did become apparent by five years after resection (odds ratio=2.291, 1.002-5.246, 95% CI).

Conclusions

There are few observation-controlled prospective randomized trials of adjuvant therapy following pancreatectomy for adenocarcinoma and very few withstand scrutiny. Though very few in numbers, together these trials assert that adjuvant therapy after pancreatectomy for adenocarcinoma improves long-term survival and should be applied. All patients undergoing pancreatectomy for adenocarcinoma should be considered for adjuvant therapy.

Poster #38: **PATIENT DEMOGRAPHICS AND SURGEON VOLUME IN PANCREATIC RESECTION MORTALITY**

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Improved outcomes after pancreatic resection (PR) by high volume (HV) surgeons have been reported in single center studies which may be confounded with potential selection and referral bias. We attempted to determine if improved outcomes by HV surgeons are reproducible when patient demographic factors are controlled at the population level.

METHODS: Using the Nationwide Inpatient Sample (NIS), discharge records for all non-trauma PR (n=3,705) were examined from 1998-2005. Surgeons were divided into two groups: high volume (HV; ≥ 5 operations / year) or low volume (LV; < 5 /year). The Elixhauser index adjusted for patient comorbidity. We created a logistic regression model to examine the relationship between surgeon type and operative mortality while accounting for patient and hospital factors. To further eliminate differences in cohorts and determine the true effect of surgeon volume on mortality, case-control groups based on patient demographics were created using propensity scores.

RESULTS: 128 HV and 1,329 LV surgeons performed 3,705 PR in 449 hospitals across 11 states that report surgeon identifier information over the 8-year period. Patients who underwent PR by HV surgeons were more likely to be male, white race, and a resident of a high-income zip code ($p < 0.05$). HV surgeons had a lower unadjusted mortality compared to LV surgeons (2.5% vs. 6.8% $p < 0.0001$). Significant independent factors for in-hospital mortality after PR included increasing age, male gender, Medicaid insurance and surgery by HV surgeon (Table). Propensity scoring was used to create matched HV and LV groups; when HV surgeons performed PR an in-hospital mortality benefit was found across all groups.

CONCLUSIONS: PR by a HV surgeon in this cohort was independently associated with a 60% reduction in in-hospital mortality. Even after removal of potential selection bias in this cohort, improved outcomes were still observed after PR by HV surgeons. This case-controlled study demonstrates improved in-hospital mortality after PR may be directly related to surgeon volume.

Table: Logistic Regression of Operative Mortality

Factor	Odds Ratio	95% CI
Age	1.1	1.0 – 1.1
Female Gender	0.6	0.4 – 0.9
Black race	1.6	0.9 – 2.7
Hispanic race	1.5	0.9 – 2.7
Medicaid Insurance	2.4	1.1 – 5.5
Urgent Admission	1.5	1.0 – 2.1
Highest Income Bracket	0.9	0.6 – 1.3
Elixhauser comorbidity	1.1	0.9 – 1.2
Malignant Diagnosis	1.4	0.9 – 2.2
High volume Surgeon	0.4	0.3 – 0.6

Poster #39: **FOCAL ADHESION KINASE IS A KEY REGULATOR OF PANCREATIC CANCER CELL MIGRATION**

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BACKGROUND: Growth factor receptors, integrins, vitronectin (VN), and focal adhesion kinase (FAK) mediate cell migration in pancreatic cancer. However, the cooperation between these different molecules in regulating pancreatic cancer cell migration is not well characterized.

METHODS: Transwell migration assays were performed with the human pancreatic cancer cell line L3.6pl. Cells were pretreated with IgG, α V β 5, or α V β 3 inhibitory antibodies (ab) then treated with phosphate buffered saline (PBS), insulin-like growth factor-I (IGF-I), or hepatocyte growth factor (HGF). To evaluate the effect of VN on growth factor-mediated migration, chambers were coated with VN or left uncoated then stimulated with PBS, IGF-I, or HGF. To evaluate the role of FAK in IGF-I-mediated migration, cells were pretreated with DMSO or FAK inhibitor (PF-562,271) then stimulated with PBS or IGF-I. To evaluate cell signaling, cells were pretreated with FAK inhibitor or α V β 5 ab, then stimulated with IGF-I, HGF, or VN, and then subjected to Western blotting for pFAK and total FAK.

RESULTS: IGF-I and HGF led to a 7.0 +/- 0.2-fold ($p < 0.0001$) and 7.0 +/- 0.3-fold ($p < 0.0001$) increase in cell migration, respectively. α V β 3 ab did not affect migration, whereas α V β 5 ab decreased IGF-I- and HGF-mediated migration by 29% +/- 3% ($p < 0.0001$) and 20% +/- 5% ($p < 0.005$), respectively. VN alone led to a 2.0 +/- 0.2-fold ($p < 0.0001$) increase in migration and augmented IGF-I- and HGF-mediated migration by 54% +/- 3% ($p < 0.0001$) and 62% +/- 5% ($p < 0.0001$), respectively. FAK inhibitor decreased IGF-I-mediated migration by 43% +/- 8% ($p = 0.005$). IGF-I and HGF increased FAK phosphorylation and this was blocked by the FAK inhibitor. VN increased FAK phosphorylation and this was blocked by α V β 5 ab.

CONCLUSIONS: FAK signaling regulates pancreatic cancer cell migration induced by IGF-I, HGF, and VN in an α V β 5-dependent manner. A better understanding of this complex signaling will help devise rational combinations of targets for therapy.

Poster #40: **PROTEOMICS-BASED APPROACH IDENTIFYING NOVEL AUTOANTIBODIES IN PATIENTS WITH PANCREATIC CANCER.**

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Introduction: To improve survival of patients with pancreatic cancer, both early detection and development of new therapeutic modalities are mandatory. Detection of novel autoantibodies in patients with pancreatic cancer may be of great value in early detection and development of new therapeutic modalities. The purpose of this study was to identify candidates for novel autoantibodies in patients with pancreatic cancer by a proteomics-based approach.

Methods: Proteins extracted from pancreatic cancer cell lines (ASPC-I and MIAPAK-II) were separated by two-dimensional PAGE, followed by Western blot analysis in which sera of 10 patients with sporadic pancreatic cancer, three patients with familial pancreatic cancer, and 8 healthy controls were tested for primary antibodies. The two-dimensional gel was stained with silver nitrate and the pieces of gel corresponding to Western blot-positive spots were excised. Extracts from gel pieces were processed through enzymatic digestion and analyzed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/TOF MS). Results: A 30-kDa spot was yielded in 6 of 10 patients with sporadic pancreatic cancer, in none of familial pancreatic cancer patients, and in one of 8 healthy controls. We identified the spot as a pancreatic cell-specific calcium-binding protein (Protein X) by MALDI-TOF/TOF MS (Figure).

Conclusion: We have first identified an autoantibody against Protein X in sera from patients with sporadic pancreatic cancer patients. Protein X is a candidate for a novel tumor marker of pancreatic cancer.

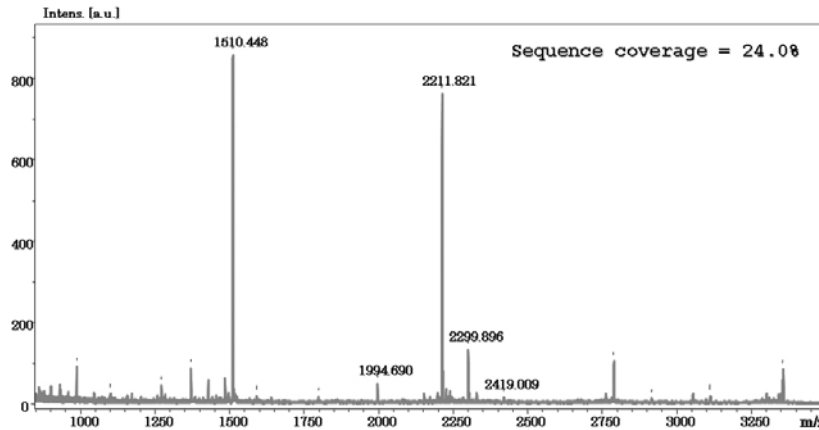


Figure: Matrix-assisted laser desorption ionization mass spectra of extracts from a 30-kDa protein spot identified in serum of a patient with pancreatic cancer. Numbers indicated m/z of tryptic digests of Protein X.

Poster #41: IDENTIFICATION OF A NOVEL KINDRED WITH FAMILIAL PANCREATITIS AND PANCREATIC CANCER

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Background/Introduction: Hereditary pancreatic cancer comprises up to 10% of pancreatic cancer cases. Prior work has identified multiple mutations that are associated with hereditary pancreatic cancer, including those forms associated with pancreatitis. Here we describe Family Pancreatitis/Pancreatic Cancer (Family P/PC), who demonstrates pancreatitis and pancreatic cancer, resulting from a previously uncharacterized genetic mutation.

Methods: Twenty-three affected and unaffected members of Family P/PC completed clinical, hematologic, radiologic, and endoscopic evaluations to determine characteristic signs of mutation status. Selected patients were screened for known genetic mutations associated with hereditary pancreatic diseases.

Results: There are approximately 140 known members of Family P/PC. In Generation II, 12 siblings demonstrate 6 cases of pancreatitis and 3 cases of pancreatic cancer. Two are obligate carriers. The average age of pancreatic disease diagnosis in enrolled members is 32.5 years, with the youngest diagnosis at 6 years. The average age of pancreatic cancer diagnosis is 59 years, with the youngest diagnosis at 45 years. There is no evidence of association of pancreatic disease with known cancer syndromes. Clinical symptoms include mild epigastric pain with abnormalities in lipase. CT scans of affecteds demonstrate a characteristic fatty infiltration of the body and tail of the pancreas with sparing of the head and neck. Full sequence analysis of genes known to be associated with hereditary pancreatic disease—*PRSS1*, *SPINK1*, *CFTR*, *BRCA1*, and *BRCA2*—failed to demonstrate known mutations or polymorphisms.

Discussion/Conclusions: Based upon pedigree evaluation and preliminary DNA analysis, we believe that the members of Family P/PC carry a novel genetic mutation resulting in hereditary pancreatitis. This mutation is transmitted in an autosomal dominant fashion, is expressed with high penetrance, and is part of a unique familial pancreatic disease syndrome that places affected members at a significantly greater risk of developing pancreatic cancer.

Poster #42: **PANCREATIC EXOCRINE FUNCTION IS PRESERVED AFTER DISTAL PANCREATECTOMY, AS ASSESSED BY HUMAN STOOL ELASTASE-1**

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Introduction: What impact does distal pancreatectomy have on pancreatic exocrine function? With the recent ability to measure human stool elastase-1 (HSE-1), the evaluation of exocrine insufficiency has become less complex. The test has a negative predictive value of almost 100%. Our previous studies have suggested that pancreatic insufficiency after pancreaticoduodenectomy is caused by exocrine atrophy from pancreatic cancer and/or parenchymal loss from resection. Our objective was to use HSE-1 to determine exocrine function after distal pancreatectomy (DP) - this has not previously been studied.

Methods: During a 67 month period after HSE-1 became available (July 2002 - January 2008), 105 patients underwent DP by the same surgeon. The pathologic tissue diagnosis and the amount of pancreas resected were recorded. Extent of resection was divided into two categories, those limited to the left of the portal vein (PV) and those extending over the PV or further. HSE-1 values were measured preoperatively in 73 patients and repeated at 3 ± 2 months, 12 ± 3 months, and 24 ± 6 months in 41, 20, and 10 patients, respectively. HSE-1 was expressed as abnormal at ≤ 200 $\mu\text{g/g}$ stool.

Results: The most common pathologic tissue diagnoses were serous cystadenoma and IPMN, each with 25% of patients, followed by islet cell tumor (15%), pancreatic adenocarcinoma (11%), chronic pancreatitis (8%), mucinous cystadenoma (8%), and other disease (8%). Preoperative HSE-1 values were abnormal in 18% of patients prior to undergoing DP (67% if chronic pancreatitis, 38% if pancreatic adenocarcinoma, and 10% in all other diseases; $p \leq 0.001$). In patients with normal preoperative exocrine function ($n=60$), postoperative HSE-1 levels were then compared to the amount of pancreas resected. At three months after resection, HSE-1 was normal in all patients if resection was to the left of the PV and in 84% of patients if resection extended over or beyond the PV ($p=0.10$). At 12 months, normal HSE-1 was observed in 100% of patients regardless of the extent of resection. At 24 months, our limited results showed normal exocrine function in 100% of patients, again regardless of the extent of resection.

Conclusion: Of patients undergoing DP, one-fifth will have pancreatic insufficiency, most commonly those with pancreatic adenocarcinoma or chronic pancreatitis. Postoperative pancreatic insufficiency was seen only transiently and only in those with resection that extended over or beyond the PV. If exocrine function was normal preoperatively, then any extent of DP remained normal or returned to normal after 3 months.

Poster #43: **MANAGEMENT OF THE PANCREATIC STUMP IN THE MODERN ERA**

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Introduction/background: pancreatic leak continues to complicate distal pancreatic resection. In december of 2000, laparoscopic pancreatic resection made its debut at our institution and now is considered for every suitable patient. With the advent of minimally invasive laparoscopic surgery, new devices and technologies, and numerous studies on various techniques to decrease fistula formation, the aim of this study is to look at our institutions various practice patterns and ultimate outcomes for distal pancreatic resection with a focus on various techniques in the management of the pancreatic stump and subsequent leak rate in an effort to identify any potential possibilities

Methods: a retrospective analysis of all hospital records was performed for all patients undergoing distal pancreatectomy from 12/2000 to 1/2008. Leaks were retrospectively classified according to the strict guidelines set forth by the isgpf. Statistical analysis was performed using chi-square two-tailed analysis of categorical and numerical variables. Comparison between subgroups was performed with case controls and were evenly matched.

Results: in total we identified 581 patients with 570 open and 71 laparoscopic resections. Indications for resection were: neuroendocrine tumors 40%, cystic neoplasms 23%, solid tumors 15%, chronic pancreatitis 8%, metastatic lesions 6%, secondary malignancies 6%, and miscellaneous 2%. Splenectomy was performed in 93.5% of cases and nearly half of cases required resection of 1 or more organs other than splenectomy or cholecystectomy (i.e. hepatectomy, colectomy, gastrectomy, etc.). Looking at patterns of pancreatic transection, 50% of surgeons used staplers for transection of the pancreas, 36% electrocautery, 6% harmonic ultrashears, 6% tissuelink, and 2% with sharp scalpel. Management of the stump after transection was varied with 79% oversewing a visible duct and/or the parenchyma with either silk, prolene, pds, maxon, or vicryl in decreasing order of frequency with 34% using a combination of suture types. Tissuelink was used in 19% to treat the stump after transection. The majority (90%) of surgeons place drains routinely. The overall leak rate in this population was 31%. Subgroup univariate analysis failed to find a significant difference in leak rates with transection method or suture types. There was a significantly lower leak rate in patients without drain placement ($p < 0.001$) corroborating work of others. Comparing tissuelink to traditional methods revealed a significantly lower leak rate ($p = 0.004$) which was reduced by 33.3%. When tissuelink treated stumps that were oversewn were compared to those that were treated alone there was a more striking decrease in leak rates (14.5%) which was also statistically significant ($p = 0.02$) and in line with our results from our previously published animal model suggesting sutures should not be placed in treated tissue.

Discussion/conclusion: in an era of change and ever evolving technology the persistent challenge of management of the pancreatic stump after distal pancreatectomy continues. The results of our large series identified one such technology that perhaps may assist in decreasing the rate of this complication.

Poster #44: **LACK OF AGGRESSIVE EARLY FLUID RESUSCITATION IS ASSOCIATED WITH ORGAN FAILURE IN ACUTE PANCREATITIS**

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AIMS: Early, aggressive fluid resuscitation is recommended for the treatment of acute pancreatitis. Our aim was to evaluate the impact of initial intravenous fluid resuscitation rate on important outcomes in acute pancreatitis.

METHODS: All patients admitted sequentially not in transfer to Mayo Clinic Rochester from July 1st 2004-June 30th 2005th with a primary diagnosis of acute pancreatitis were prospectively identified. Only patients with prospectively recorded IV fluid volumes were included. Patients were divided into two groups – those who received $\geq 33\%$ (“aggressive”) and $< 33\%$ (“non-aggressive”) of their cumulative 72 hour intravenous fluid volumes within the first 24 hours of admission. The primary outcomes of interest were the development of organ failure, length of hospital stay longer than 10 days and admission to the ICU. Student’s t- and chi-squared tests were used to compare groups and conditional logistic regression was used to evaluate for confounding. The study was approved by the Mayo IRB.

RESULTS: 73 patients were identified – 42 in the “aggressive” group and 31 in the “non-aggressive” group. There were no baseline differences in age, gender, BMI, admission APACHE II or SIRS scores between groups. 5 patients died in the hospital; 10 developed organ failure; 14 stayed longer than 10 days; 7 were admitted to the ICU. Compared to the “aggressive” group, patients in the “non-aggressive group” developed significantly higher rates of organ failure (22.6% vs. 7.1%, $p<0.03$) and trended toward longer hospital stays (25.8% vs. 14.3%, $p=0.11$) and higher rates of ICU admission (12.9% vs. 7.1%, $p=0.20$). There was no difference in the cumulative 72 hour IV fluid volume between groups (“aggressive” = 5,699 ml vs. “non-aggressive” = 6,716 ml, $p=0.075$) although the “aggressive” group did receive more IV volume within the first 24 hours (2,864 ml vs. 1,725 ml, $p<0.001$). Conditional logistic regression revealed no confounding when controlling for admission APACHE 2 and SIRS scores.

CONCLUSIONS: In a population of patients admitted sequentially with acute pancreatitis, less aggressive initial intravenous fluid resuscitation rate in the first 24 hours of admission was associated with significantly higher rates of organ failure, and a trend toward longer hospitalizations and more frequent ICU admission. Prospective, controlled studies are needed to validate this finding.

Poster #45: **PREDICTION OF MALIGNANCY AND SURVIVAL USING QUALITY OF LIFE MEASURES IN PATIENTS WITH PANCREATIC PATHOLOGY**

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Background: It is common to use quality of life (QoL) measures to assess treatment outcomes for pancreatic disease. However, in other disease processes, it has been suggested that pretreatment QoL scores can predict the outcome of treatment; specifically, in some malignant diseases, QoL can predict survival. This study assessed whether pre-treatment QoL scores could predict malignancy in patients with pancreatic lesions and survival in those with malignancies.

Methods: Patients for surgery with pancreatic lesions completed the SF-36, which contains 8 domains measuring QoL: physical functioning (PF), role-physical (RP), role-emotional (RE), bodily pain (BP), vitality (VT), mental health (MH), social functioning (SF), and general health (GH). Best possible score is 100, worst possible score is 0. Patients with pain related to known chronic pancreatitis were excluded from the study; however, undiagnosed solid or cystic lesions were included. Data obtained included age, gender, resectability, additional antineoplastic therapy, stage, pathology, and survival. Patients were categorized by pathology (benign vs. malignant), stage (local, regional or distant), resectability (resected vs. not), survival (<1 yr. vs. >1yr.) and their pretreatment QoL scores. Data was analyzed by the Mann-Whitney U-test and multiple logistic regression.

Results: Of the 178 patients assessed, 108 had malignancies. In 6 of the 8 domains, patients with malignancies had lower median QoL scores compared to patients with benign lesions: PF 55 vs 85 ($p=0.01$), RP 0 vs 75 ($p=0.005$), RE 67 vs 100 ($p=0.05$), BP 61.5 vs 63 ($p=0.008$), VT 40 vs 55 ($p=0.01$), and SF 62.5 vs 87.5 ($p=0.02$). Of the patients with malignancies, patients surviving ≤ 1 yr. had lower pretreatment scores in 6 of 8 domains (PF 40 vs 67.5, RP 0 vs 25, BP 51 vs 62, VT 25 vs 52.5, MH 68 vs 80, and SF 50 vs 75, all $p \leq 0.05$). By multiple logistic regression, stage, VT score and MH score were predictive of survival < 1yr.

Conclusions: Patients with pancreatic malignancies had lower QoL scores than patients with benign pancreatic disease. This suggests that QoL scores may help select which patients have benign disease and therefore could safely avoid resection. Patients with malignancies surviving ≤ 1 yr. had lower scores, even after controlling for stage. These lower scores may reflect more advanced disease or frailties which identify patients with poor prognoses. This suggests that pretreatment QoL scores may be used to predict which patients will have a poor survival and therefore could avoid aggressive, but futile, treatment.

Poster #46: **COMPARISON OF ASPIRATE CEA AND DNA ANALYSIS IN 100 CONSECUTIVE PATIENTS WITH PANCREATIC CYSTS**

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Background: Pancreatic cyst fluid CEA levels and DNA analysis have been proposed as useful diagnostic tests in differentiating mucinous from non-mucinous cysts. However, studies directly comparing these two approaches are lacking. We sought to compare the CEA level with DNA analysis of pancreatic cyst aspirates obtained by EUS. **Methods:** Patients were identified who underwent EUS-FNA for evaluation of pancreatic cysts from 2006 – 2007. Those with acute pancreatitis within 4 months were excluded. A cyst was designated as mucinous by either: CEA criteria - level ≥ 192 ng/ml, or DNA analysis criteria – DNA quantity ≥ 40 ng/ul and/or k-ras-2-point mutation and/or ≥ 2 allelic imbalance mutations. Pathologic analysis of resected cysts served as the reference standard. **Results:** 100 consecutive patients met study criteria. The average age was 63 years, 65% were women, and 30% were symptomatic. The mean cyst diameter was 26mm (long-axis) x 19mm (short-axis). Forty-three percent of cysts were in pancreatic head/uncinate, 17% had an intrinsic nodule /mass, and 44% were multi-loculated. Cytology was atypical, suspicious, or diagnostic of malignancy in 10%. Of the 84 patients for whom results of both CEA and DNA analysis were available, the median CEA value was 83ng/ml [range1-50,000], mean DNA content was 16ng/ul [range1-212], 11% had k-ras mutations, and 43% had ≥ 2 allelic imbalance mutations. Using pre-specified criteria, there was poor agreement between CEA and overall DNA analysis [considering all 3 aspects together] for the classification of mucinous and non-mucinous cysts [Kappa= 0.2]. Poor to fair agreement existed between CEA and DNA quantity [Spearman's correlation=0.2; p=0.1], k-ras mutation [kappa=0.3] and ≥ 2 allelic imbalance mutations [kappa=0.1]. Final pathological diagnosis was available for 19 patients. CEA had an accuracy of 84% compared with 79% for DNA analysis for correctly identifying mucinous cysts (Table 1). When CEA level and DNA analysis were combined, 100% accuracy was achieved. **Conclusion:** Pancreatic cyst fluid CEA and DNA analyses appear to measure different features of cyst biology. Considering both together may improve diagnostic accuracy of EUS-FNA in delineating mucinous cysts.

Table 1: Test characteristics for differentiating mucinous cysts using CEA and DNA analysis from EUS-based aspirates

	Sensitivity	Specificity	Accuracy
CEA ¹	82%	100%	84%
DNA Analysis (Overall) ²	77%	100%	79%
DNA Quantity ³	29%	100%	37%
K-ras mutation	11%	100%	21%
Allelic Imbalance	70%	100%	73%

1 = For CEA level of 192 ng/ml.

2 = Using criteria specified in methods section

Poster #47: **GEMCITABINE-BASED ADJUVANT CHEMOTHERAPY IMPROVES SURVIVAL FOR PATIENTS WITH LOCALLY-ADVANCED PANCREATIC CANCER**

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Background: Radical resection (R0) is the surgical goal in pancreatic cancer surgery, but it often results in R1 resection. Recent RCTs for adjuvant chemotherapy with gemcitabine (GEM) showed survival benefit not only in patients with R0 resection but also in patients with R1 resection, e.g. median survival time (MST) was 22.1 months in patients with R1 resection using GEM compared with 14.1 months in observation arm in CONKO-001 trial. We evaluated the role of adjuvant chemotherapy with gemcitabine in pancreatic cancer treatment.

Methods: We reviewed the data of 240 patients who underwent pancreatic resection with curative intent for pancreatic cancer in Teikyo university hospital during 1981-2007. Pancreaticoduodenectomy was performed in 68%, distal pancreatectomy in 19% and total pancreatectomy in 13%. Combined major vascular resection was performed in 124 patients (52%). R0 resection was achieved in 62%, R1 was in 21%, and R2 was in 12%. Sufficient R status information was not available in 5% and these cases were excluded from analysis. Adjuvant chemotherapy with GEM was used in 56%. Kaplan-Meier survival curve was calculated and survival was compared by log-rank test.

Results: Mortality was 2.9%. Morbidity was 37%. MST for entire cohort was 18 months and 5-year survival rate was 15.9%. Survival comparing patients with GEM versus without GEM significantly different (MST: 22 vs. 13 months, P=0.003). Survival for patients having had R1 and R2 resection was significantly improved by the use of GEM-based adjuvant chemotherapy (Table).

	MST w/ GEM (m)	MST w/o GEM (m)	P
R0	25 (N=86)	28 (N=61)	n.s.
R1	22 (N=30)	8 (N=21)	< 0.001
R2	9 (N=13)	3 (N=16)	0.006

Conclusion: Gemcitabine-based adjuvant chemotherapy significantly improves survival in patients with R1 resection approaching to the survival of patients with R0 resection (MST: 22 vs. 25 months). This result would support more radical surgical approach, such as combined vascular resection in the management of locally-advanced pancreatic cancer as long as surgical mortality, morbidity and patient's quality of life is acceptable.

Poster #48: **EXOGENOUS INTRODUCTION OF PP32 EXPRESSION IN POORLY-DIFFERENTIATED PANCREATIC CANCER CELLS RESULTS IN GROWTH CESSATION AND CHEMOSENSITIZATION**

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Background: It is known that multiple genetic alterations and changes in gene expression are required for the development of pancreatic cancer. Some of the common genes affected include p16, k-ras, p53, and Smad 4. As we have previously reported, the expression of pp32 (a tumor suppressor protein) is present in well-differentiated tumors, but is dramatically reduced or absent in poorly-differentiated tumors. Thus, it may play an integral role in the process of pancreatic tumorigenesis for poorly differentiated pancreatic ductaladenocarcinoma (PDA). Further, pp32 has been shown to inhibit k-ras in experimental models. We hypothesized that exogenously introducing pp32 may reduce the aggressiveness of this subset of pancreatic tumors, making this a favorable target for gene therapy. Additionally, we hypothesized that exogenously introducing pp32 expression may sensitize these cells to chemotherapeutics used against pancreatic cancer, such as 5-fluorouracil.

Study Design: Using a eukaryotic plasmid vector system, the poorly-differentiated PDA cell line MiaPaCa was stably transfected with pp32 *in vitro*. Overexpression was confirmed using RT-PCR, Western blot, and immunofluorescence analysis. Flow cytometry was performed to evaluate for changes in cell cycle parameters in the overexpressing versus the empty vector cell lines. Additionally, growth potential of the MiaPaCa pp32 overexpressing cells (Mia.pp32) compared to empty vector cells (Mia.EV) was assessed using a cell proliferation assay. Cells were equally plated into flasks, then collected and counted at specified time points. As a control, pp32 was introduced into a chromosomally stable, moderately differentiated pancreatic cancer cell line (PL5). Finally, Mia.pp32 and Mia.EV cells were equally plated into 96-well plates and treated with various concentrations of 5-FU. Subsequently, a cell survival assay was performed using PicoGreen staining, which provides a quantitative assessment of dsDNA content within a sample.

Results: Flow cytometric cell cycle analysis demonstrated a G0/G1 cell cycle arrest in Mia.pp32 relative to Mia.EV when grown to 100% confluence. There was also a dramatic difference in growth, as demonstrated by a cell proliferation assay. At each time point, Mia.pp32 cell counts were significantly lower than that of Mia.EV, with five-fold fewer Mia.pp32 cells at the final time point. As a control, a moderately differentiated pancreatic cancer cell line (PL5) showed only a modest reduction in growth rate when pp32 was exogenously overexpressed. Furthermore, Mia.pp32 demonstrated a significantly increased sensitivity to 5-FU compared to Mia.EV at physiologic concentrations. The IC-50 values for Mia.pp32 and Mia.EV were 0.9 μ M and 2.5 μ M respectively. **Conclusions:** These data provide the first descriptive evidence that introduction of pp32 expression reduces cell growth potential of poorly differentiated pancreatic cancer cells. Additionally, restoration of pp32 expression in MiaPaCa cells increases sensitivity to 5-FU. The exact mechanism by which pp32 is inhibiting poorly-differentiated pancreatic cancer cells and sensitizing them to 5-FU is currently being explored. This work provides evidence that introduction of pp32 expression may be a favorable therapeutic intervention in the most aggressive type of pancreatic cancers. Further, it provides evidence that the loss of pp32 expression represents a critical step in the process of tumorigenesis for poorly-differentiated pancreatic cancer.

Poster #49: **CANNABINOID RECEPTOR BLOCKADE ATTENUATES ACUTE PANCREATITIS BY AN ADIPONECTIN MEDIATED MECHANISM**

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BACKGROUND: Obesity is an independent risk factor for developing severe acute pancreatitis. Adipose tissue produces hormones (adipokines) that regulate metabolism and inflammation. We recently showed that the potent anti-inflammatory adipokine adiponectin inversely mirrors the severity of acute pancreatitis in lean and congenitally obese mice. Increased circulating adiponectin concentration is observed after central blockade of the cannabinoid-1 (CB-1) receptor. We hypothesized that CB-1 blockade would increase adiponectin concentration and attenuate the severity of acute pancreatitis.

METHODS: 32 congenitally obese (Lep^{db/db}) mice were studied at 16 weeks of age. Half of the mice were subjected to acute pancreatitis by cerulein injection (50µg/kg IP hourly X 6); the others received saline. For 7 days prior to study, half of the animals in each group (pancreatitis/control) received the CB-1 receptor antagonist rimonabant (10mg/kg IP); the other half received vehicle. Mice were sacrificed 9 hours after pancreatitis induction. Histologic pancreatitis severity was determined by a validated method. Serum adiponectin concentration and pancreatic concentration of the pro-inflammatory cytokine interleukin-6 (IL-6), and the chemoattractant molecule MCP-1 were measured by ELISA. ANOVA and Tukey's test were applied where appropriate; p<0.05 was considered statistically significant.

RESULTS: CB-1 blockade with rimonabant significantly increased circulating adiponectin levels (p<0.05, Table). In the control group, treatment with rimonabant did not change pancreatic levels of IL-6 or MCP-1. In the pancreatitis group, CB-1 blockade with rimonabant significantly decreased the histologic pancreatitis score (p<0.001) as well as pancreatic IL-6 and MCP-1 expression (p<0.001) compared to vehicle treated animals.

	CONTROL		PANCREATITIS	
	Vehicle	Rimonabant	Vehicle	Rimonabant
Adiponectin (µg/mL)	2.2 ± 0.3	4.1 ± 0.6 [†]	2.9 ± 0.4	4.8 ± 0.8 [†]
Pancreatitis Score	0.2 ± 0.5	0 ± 0	7.6 ± 1.0	2.9 ± 0.9 [†]
IL-6 (pg/mL)	231 ± 58	237 ± 148	3445 ± 1432	373 ± 52 [†]
MCP-1 (pg/mL)	380 ± 51	293 ± 66	7740 ± 1386	2096 ± 239 [†]

[†]p<0.05 vs vehicle in each group (control/pancreatitis); [†]p<0.001 vs vehicle within pancreatitis group

CONCLUSION: These data demonstrate that CB-1 receptor blockade 1) increases circulating adiponectin and 2) significantly attenuates the severity of acute pancreatitis in congenitally obese mice. We conclude that the adipokine milieu is important in the pathogenesis of severe acute pancreatitis in obesity, and that CB-1 blockade attenuates acute pancreatitis by an adiponectin mediated mechanism.

Poster #50: INFECTION WITH RESISTANT BACTERIA AND YEAST DRAMATICALLY INCREASES MORBIDITY AND MORTALITY IN PATIENTS WITH NECROTIZING PANCREATITIS.

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INTRODUCTION: Empiric broad-spectrum antibiotic treatment is applied commonly to patients with necrotizing pancreatitis (NP), though current data have challenged the efficacy of this practice. This treatment strategy clearly leads to a shift in the predominant infectious organisms from enteric Gram-negative to Gram-positive, resistant bacteria (MRSA, VRE), and yeast. We hypothesized that infection with resistant bacteria and yeast would result in poorer clinical outcomes in patients with NP.

METHODS: Review of 152 patients with NP (1992 – 2007) compared those with and without resistant bacteria and yeast infection. Student's t-test and χ^2 were applied where appropriate, with $p < 0.05$ considered significant.

RESULTS: Of 152 patients with NP, 86 (57%) grew resistant bacteria and 64 (42%) grew yeast in one or more organ systems (table). Patients with resistant bacterial infection had significantly increased length of stay, number of reoperations and number of readmissions ($p < 0.05$) compared to those who did not develop resistant bacterial infection. Patients with yeast infection had significantly increased length of stay, number of reoperations, and mortality ($p < 0.05$) compared to those without yeast infection.

	Resistant Bacteria		Yeast	
	Non-Resistant	Resistant	No Yeast	Yeast
NUMBER	66 (43%)	86 (57%)	88 (58%)	64 (42%)
LENGTH OF STAY	33 (4-145)	53 (12-179)*	35 (4-145)	58 (12-179)*
REOPERATIONS	0.6 (0-6)	1.5 (0-6)*	0.9 (0-4)	1.4 (0-6)*
READMISSION	1.3 (0-9)	1.9 (0-7)*	1.4 (0-9)	1.9 (0-8)
DEATH	5 (8%)	12 (14%)*	5 (6%)	12 (19%)*

Data are mean \pm (% or range), * $p < 0.05$ vs. Non-Resistant or No Yeast group.

CONCLUSIONS: These data show that in patients with NP: 1) Infection with resistant bacteria leads to significantly increased length of stay, reoperation rate, and readmission, and 2) Fungal infection is associated with significant increase in length of stay, need for reoperation and death. Given these findings, we recommend reserving antibiotic therapy for documented infection, and abandoning the routine practice of administering broad-spectrum "prophylactic" antibiotics to patients with necrotizing pancreatitis.