

1. EARLY SURGERY VERSUS CURRENT STEP-UP PRACTICE FOR CHRONIC PANCREATITIS: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Background: Surgical intervention for chronic pancreatitis is currently used as last resort treatment when the first steps of the step-up approach, medical and endoscopic treatment have both failed. It has been suggested that early surgery may lead to better pain relief and preservation of pancreatic function, as compared to the current step-up approach. We conducted a randomized controlled trial to compare early surgery with the current step-up approach.

Methods: We included patients with chronic pancreatitis according to the MANNHEIM criteria, a dilated pancreatic duct (≥ 5 mm) and severe continuous or frequent intermittent pain, who recently started treatment with opioids. Patients who used strong opioids for more than 2 months or weak opioids for more than 6 months in the last 2 years were excluded. Patients were randomly assigned to early surgery (i.e. 6 weeks after randomization) or to the step-up approach (step 1: medical treatment, if needed, step 2: endoscopic intervention, if needed, step 3: surgical intervention). The primary endpoint was the mean Izbicki pain score during 18 months of follow-up. Secondary endpoints included pain relief, complications, mortality, number of interventions, pancreatic function, and quality of life.

Results: Eighty-eight patients were randomized, 44 to early surgery (41 underwent surgery) and 44 to the step-up approach (44 underwent medical treatment, 39 endoscopic intervention, and 13 surgical intervention). Patients in the early surgery group had a lower mean Izbicki pain score during follow-up, as compared to patients in the step-up approach (35 vs. 48, $P=0.018$). Taken into account the baseline pain score, early surgery showed a larger decrease in Izbicki pain score during follow-up (-26 vs. -16, $P=0.04$). Complete or partial pain relief during follow-up was achieved in 54% of patients in early surgery and in 33% of patients in the step-up approach (RR: 1.52 [1.40-1.66], $P<0.001$). Fewer interventions were performed in the early surgery group compared to the step-up group (median 1 vs. 3, $P<0.001$). Complications, mortality (0%), hospital readmission, pancreatic function and quality of life were comparable among groups.

Conclusion: The preferred treatment strategy for patients with chronic pancreatitis and a dilated pancreatic duct is early surgery within the first months of opioid use, because this provides better pain relief with less interventions than the current step-up approach.

2. MINIMALLY INVASIVE SURGERY VERSUS ENDOSCOPY RANDOMIZED TRIAL FOR NECROTIZING PANCREATITIS

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Background: Necrotizing pancreatitis is a highly morbid disease with poor outcomes and the treatment strategy has evolved from open necrosectomy to minimally-invasive approaches. We compared minimally-invasive surgery and endoscopic approaches for interventions in necrotizing pancreatitis.

Methods: Patients with necrotizing pancreatitis requiring interventions were randomly assigned to minimally-invasive surgery or endoscopic treatment approaches. The primary endpoint was to compare a composite of major complications (new onset multi-organ failure, new onset systemic dysfunction, enteral or pancreatic-cutaneous fistula, bleeding and perforation of visceral organ) or death during 6-month follow-up.

Results: 66 patients underwent surgical (n=32) or endoscopic (n=34) interventions. The primary outcome occurred in 11.8% of endoscopic and 40.6% of surgical cohorts (risk ratio, 0.29; 95% confidence interval, 0.11-0.80, p=0.007). While there was no significant difference in mortality (endoscopy 8.8% vs. surgery 6.3%; p=0.999), patients assigned to the endoscopic approach did not develop enteral or pancreatic-cutaneous fistulae (0 vs. 28.1%; p=0.001). The mean number of major complications per patient was significantly higher for surgery as compared to endoscopy (0.69 [SD=1.03] vs. 0.15 [SD=0.44]; p=0.006). The physical health scores for quality of life at 3 months was better (p=0.039) and mean total cost was lower (\$75,830 vs. \$117,492; p=0.039) for the endoscopic approach.

Conclusion: Endoscopic interventions, as compared to minimally invasive surgery, reduce the rate of composite endpoint of major complications among patients with necrotizing pancreatitis, were associated with better physical health and lower costs.

3. AUTOLOGOUS MESENCHYMAL STEM CELL AND ISLET CO-TRANSPLANTATION: SAFETY AND EFFICACY

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Background: Islet engraftment after transplantation is impaired by high rates of islet/ beta cell death caused by cellular stressors and poor graft vascularization. We studied whether co-transplantation of ex vivo expanded autologous bone marrow-derived mesenchymal stem cells (MSCs) with islets is safe and beneficial in chronic pancreatitis patients undergoing total pancreatectomy with islet autotransplantation (TPIAT).

Methods: With IRB approval, MSCs AQ4 were harvested from the bone marrow of three islet autotransplantation patients and expanded at our cGMP facility. On the day of islet transplantation, an average dose of $20 \pm (2.6 \times 10^6)$ MSCs was infused with islets via the portal vein. Adverse events and glycemic control at baseline, 6, and 12 months after transplantation were compared with data from 101 historical control patients.

Results: MSC patients required lower amounts of insulin during the peri-transplantation period ($p = 0.02$ vs. controls), had lower 12 month fasting blood glucose levels ($p = 0.02$ vs. controls), smaller C-peptide declines over 6 months ($p = 0.01$ vs. controls), and better quality of life compared with controls. No adverse events directly related to the MSC infusion were observed.

Conclusion: This pilot study demonstrates for the first time that intrahepatic infusion of autologous bone marrow-derived mesenchymal stem cells (MSCs) during islet transplantation may be safe and may have the potential to improve islet engraftment, glycemic control, and quality of life after TPIAT. This work extends the current paradigm of MSCs as an immune regulatory factor and reveals important additional functions of MSCs in promoting islet engraftment after TPIAT. This study proves justification for a larger and randomized clinical trial, as MSCs have the potential to reduce inflammatory damage and support angiogenesis in transplanted islets.

4. TREATMENT WITH VOLANESORSEN REDUCED TRIGLYCERIDES AND PANCREATITIS IN PATIENTS WITH FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS) AND SEVERE HYPERTRIGLYCERIDEMIA (sHTG) VS PLACEBO: RESULTS OF THE APPROACH AND COMPASS STUDIES

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Background: FCS is a rare genetic disease characterized by severe chylomicronemia, sHTG and consequent risk of potentially fatal recurrent and acute pancreatitis (AP). HTG-induced AP has a more severe course, leading to worse outcomes.

Aim: To evaluate if volanesorsen, an antisense inhibitor of APOC3, reduced pancreatitis in patients with FCS and severe HTG (sHTG) participating in two Phase-III trials.

Methods: Two Phase-III trials evaluated the effect of volanesorsen on TG reduction and AP risk in patients with FCS or sHTG. The APPROACH study included 67 FCS patients (66 received study drug) with fasting TGs ≥ 750 mg/dL randomized 1:1 to 52 weeks of weekly volanesorsen (300mg) or placebo (PBO). The COMPASS study included 114 sHTG patients (113 received study drug) with fasting TG ≥ 500 mg/dL randomized 2:1 to volanesorsen or PBO weekly for 26 weeks. Endpoints included percent reduction in plasma TGs at 3 months and treatment-emergent pancreatitis.

Results: Results from COMPASS & APPROACH combined showed a significant reduction ($p=0.0185$) in pancreatitis (1 event in 1 patient in volanesorsen group; 9 events in 6 patients in PBO group). Also, in APPROACH, patients with ≥ 2 episodes of pancreatitis in the 5 years before randomization suffered no attacks in the study treatment period ($p=0.02$). In APPROACH, TGs at month 3 decreased by 77% in volanesorsen group ($n=33$) and increased by 18% in PBO group ($n=33$) ($p<0.0001$). In COMPASS, volanesorsen decreased TGs by 73% ($p<0.0001$) ($n=75$) after 3 months, compared with 2% decrease in PBO ($n=38$). The most common AEs with volanesorsen were injection site reactions (percent of injections with at least one ISR: 12% FCS/24% sHTG). Declines in platelet counts led to 5 early terminations in APPROACH, 2 of which had platelets $< 25,000/\mu\text{l}$; platelet counts recovered to normal after volanesorsen stopped. There were no serious platelet events in COMPASS, but 1 possible related SAE reported as serum sickness occurred 2 weeks after the last study dose.

Conclusion: Volanesorsen treatment reduced TGs and consequent AP risk in FCS and sHTG patients.

5. SALVAGE MINIMALLY INVASIVE SURGERY AFTER FAILED INITIAL PERCUTANEOUS DRAINAGE AS STEP-UP APPROACH IN PANCREATIC NECROSIS: RESULTS OF A PROSPECTIVE STUDY

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Background: In our experience, the use of percutaneous drainage (PCD) in infected pancreatic necrosis led to improved outcomes and obviated the need for surgery in a significant proportion. However, prolonged use of PCD has a possibility of developing simmering sepsis, gradual nutritional depletion, and late-onset organ failure. Hence, the timing of switching from PCD to surgical intervention becomes important. We aimed to ascertain the optimal timing of intervention with video-assisted retroperitoneal debridement (VARD) and to look at mortality and morbidity in infected pancreatic necrosis managed with the two approaches.

Methods: This prospective study was conducted from July 2016 to November 2017. Patients with moderately severe and severe acute pancreatitis (revised Atlanta) who failed to improve or deteriorated within 7 days after PCD were included. Patients who did not respond to aggressive PCD management received minimally invasive surgical intervention. Primary endpoints included mortality, morbidity, and requirement of surgery.

Results: 55 patients were assessed and 36 were included. Predominant etiology was alcohol (61%). Severe acute pancreatitis was present in 88.9% (n=32). Mean APACHE and modified Marshall Score (MMS) scores at presentation were 10.3 ± 5.5 and 3.69 ± 2.6 respectively. MCTSI at time of presentation was 8.72 ± 1.66 . Both groups were comparable in terms of demographic data, APACHE II score, MMS score, MCTSI score at first CT, and incidence of infected necrosis. Overall, 63% (35/55) patients were successfully managed with PCDs alone. In those who failed initial PCD drainage, the PCD success rate was 44% (16/36). Indications for surgery included unresolved sepsis in 7 patients and colonic ischemia, bowel obstruction and flank abscess in one each. 3 patients developed PCD-related entero-cutaneous fistulae and were successfully managed conservatively. 8 surgical interventions were performed in 7 patients (VARD-6, minimal incision-2). Two patients required open necrosectomy for bowel obstruction and colonic ischemia. Patients were operated at a mean of 48.2 ± 6.6 days from onset of pain. Mean MMS remained similar between the two arms for the first 4 weeks of illness; thereafter surgery arm had higher mean MMS scores, which were significantly higher at 7 weeks of illness ($p=0.05$) (Image 1). The incidence of positive blood culture ($p=0.03$) and requirement of parenteral nutrition ($p<0.01$) were significantly more in patients who were operated. Overall mortality for the whole group was 25.4% (14/55) while mortality in PCD only group was 34.5% (10/29) and in PCD+VARD was 57.1% (4/7).

Conclusion: 63% patients were managed with PCD and irrigation alone. Mortality remained high in patients requiring surgery after extended PCD drainage.

6. CHLOROQUINE AMELIORATES PANCREATITIS THROUGH INHIBITION OF NEUTROPHIL EXTRACELLULAR TRAPS

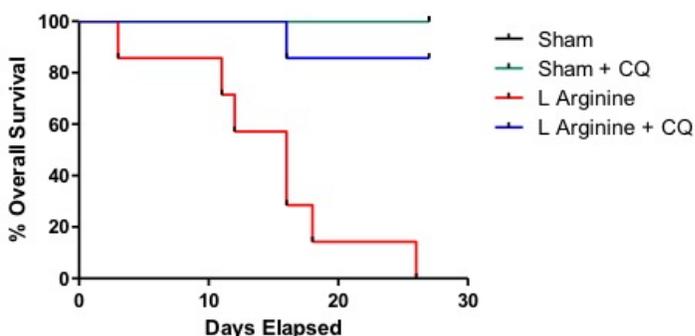
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Background: Neutrophil extracellular traps (NETs) occur when activated neutrophils release their intracellular contents, including histones, DNA, elastase and other proteins, into the extracellular space, tissues or circulation. Recently, NETs have been implicated in acute pancreatitis, worsening pancreatic inflammation, and promoting pancreatic duct obstruction. We have previously shown that the autophagy inhibitor chloroquine (CQ) inhibits NET formation; therefore we sought to determine if CQ could improve severity and outcome in murine pancreatitis through NET inhibition.

Methods: Acute pancreatitis was induced in C57/Bl6 mice through two hourly injections of L arginine (4g/kg) into the peritoneal cavity. Sham control mice were injected with saline. Mice were sacrificed 48 hours after injection to collect serum. Neutrophils were harvested from bone marrow using density gradient centrifugation and stimulated with platelet activating factor to induce NET formation. Hoechst staining of DNA was then utilized to visualize NETs using fluorescence microscopy. Citrullinated histone H3 (Cit H3), which allows for unwinding and expulsion of neutrophil DNA during NET formation and is a critical marker of NETs, was measured in murine serum using ELISA. Serum DNA was measured using Quant-It picogreen. For survival experiments, mice were injected with L arginine weekly x 3 weeks. Animals were treated with CQ in the drinking water (100 mg/kg/day PO), beginning 1 hour after induction of pancreatitis.

Results: Injection of L arginine resulted in increased serum amylase and trypsin compared with sham controls, consistent with induction of pancreatitis. Neutrophils harvested from mice with pancreatitis were more prone to NET formation than sham injected controls. Induction of pancreatitis resulted in a significant increase in serum DNA and citrullinated histone H3, suggesting upregulated *in vivo* NET formation. CQ treatment decreased the propensity to form NETs from neutrophils harvested in mice with pancreatitis. Both serum DNA and Cit H3 were significantly decreased with CQ treatment, suggesting a decrease in NETs in response to CQ. CQ lessened the severity of acute pancreatitis, resulting in a reduction in serum amylase and trypsin with CQ treatment. CQ treatment improved survival from pancreatitis (Figure 1, median survival 15 days vs. not reached, $p < 0.05$).

Conclusion: CQ treatment decreases the severity of L arginine induced murine pancreatitis through inhibition of neutrophil extracellular traps, resulting in improved survival. NET inhibition represents a novel treatment strategy in acute pancreatitis. Further study to translate these findings into human severe acute pancreatitis is warranted.



7. NECROSIS MORPHOLOGY DOES NOT PREDICT SUCCESS OF PERCUTANEOUS DRAIN IN NECROTIZING PANCREATITIS

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Background: Minimally invasive methods are increasingly utilized as the first step of treatment in Necrotizing Pancreatitis (NP). Percutaneous Drainage (PD) is often the preferred minimally invasive approach and may provide definitive therapy in up to a third of patients. Determining the timing and need to “step-up” is more an art than a science. Predictors of success or failure of PD as definitive treatment would streamline treatment algorithms in NP. Our aim was to assess the application, predictors of success, and the natural history of PD in NP; we hypothesized that specific necrosis morphology patterns may predict outcome after PD.

Methods: 647 NP patients were treated at our institution between 2005 and 2017. Patients undergoing PD as their first intervention were divided into two groups: those in whom PD achieved definitive treatment (DefPD), and those who required step-up to additional intervention (Step). Definitive treatment was defined as resolution of disease with percutaneous drainage as sole management. Resolution was defined as the removal of all percutaneous drains without requirement of further intervention. Cross-sectional imaging immediately prior to drain placement was reviewed and the presence of necrosis was recorded in six locations: head/neck; body/tail; lesser sac; left/right paracolic gutter; and root of the small bowel mesentery. Morphology patterns and outcomes were compared. Independent t-test was performed to analyze the bivariate relationships between the two groups and data points of interests. P-values of <0.05 were accepted as statistically significant.

Results: A total of 107 patients were initially managed with PD: 32 DefPD, 62 Step. Thirteen patients who died prior to disease resolution were censored. Median follow-up was 17 months (range 2-150 months). The necrosis morphology was similar between the two groups (table 1). DefPD required significantly more repeat drainage procedures (3.3 DefPD vs. 2.0 Step, $p<0.01$). Step-up occurred at a median of 3 weeks. Median time to resolution of disease was similar: 4.8 months (range 1-22) DefPD vs. 5.1 months (range 1-26) Step ($p=0.6$). Late operation, either distal pancreatectomy with splenectomy or tail pancreateojejunostomy, for disconnected tail occurred in 14% at a median of 15 months (range 4-45 months).

Conclusion: Percutaneous Drainage may act as definite therapy in a percentage of Necrotizing Pancreatitis patients. Neither necrosis morphology nor presence of disconnected pancreatic tail reliably need for step up in therapy. Long-term follow up is

critical, as a significant number of necrotizing pancreatitis patients require late operation.

	DefPD (n=32)	Step (n=62)	p-value
Gland Necrosis			
Head/Neck	47%	52%	0.62
Body/Tail	53%	54%	0.94
Peri-Pancreatic Necrosis			
Lesser Sac	97%	100%	0.16
R Paracolic Gutter	16%	22%	0.45
L Paracolic Gutter	34%	32%	0.80
Small Bowel Mesentery	28%	27%	0.91
Multi-field Necrosis	53%	60%	0.51
Disconnected Pancreatic Tail	9%	21%	0.17
Late Operation	9%	16%	0.37

8. INTERNATIONAL VALIDATION OF THE 8TH EDITION AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING SYSTEM IN PATIENTS WITH RESECTED PANCREATIC CANCER

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Background: The American Joint Committee on Cancer (AJCC) has proposed the 8th edition of the TNM staging system in pancreatic cancer in order to improve prognostic accuracy and guide treatment decisions. An international validation study in a cohort with representative heterogeneity and sufficient long-term follow-up is currently lacking. The objective of this study is to validate the proposed 8th edition of the AJCC TNM staging system in an international cohort of resected pancreatic cancer.

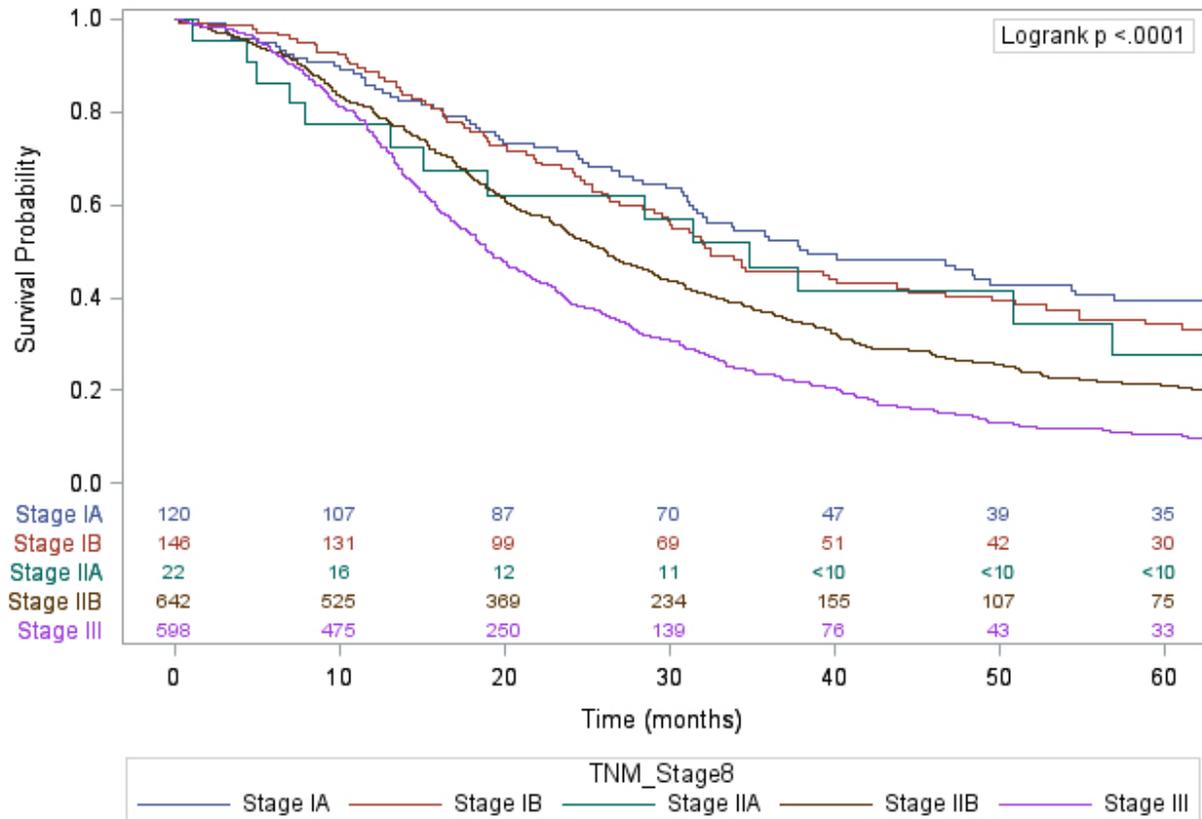
Methods: Patients who underwent pancreatoduodenectomy for non-metastatic pancreatic ductal adenocarcinoma between 2000-2015 at 5 referral centers from 4 countries were retrospectively staged according to the 8th edition of the TNM staging system, based on tumor size (T1: ≤ 2 cm, T2: >2 and ≤ 4 cm, T3: >4 cm, T4: involves celiac axis/superior mesenteric artery) and number of positive lymph nodes (N0: no positive lymph nodes (LN), N1: 1-3 positive LNs, N2: ≥ 4 positive LNs). Prognostic accuracy on overall survival was evaluated by Kaplan-Meier estimates and concordance statistics (Uno's C-statistic) with 95% confidence intervals (CI) to compare both editions of the TNM staging system.

Results: In total, 1528 patients were included for analysis. Distribution among stages changed from 2.7%, 3.0%, 13.2%, 80.4%, 0.8% in the 7th edition to 7.9%, 9.6%, 1.4%, 42.0%, 39.1% in the 8th edition for stage IA, IB, IIA, IIB and III, respectively. With the 8th edition, 781 patients (51.1%) migrated to a different stage, of whom 188 patients (12.3%) to a lower stage and 593 patients (38.7%) to a higher stage. Median overall survival for the entire cohort was 24.4 months. Five-year survival rates changed from 37.6%, 39.3%, 35.1%, 16.5%, 0% (log-rank $p < 0.0001$) in the 7th edition, to 39.4%, 34.2%, 27.6%, 21.0% and 10.8% (log-rank $p < 0.0001$) in the 8th edition for stage IA, IB, IIA, IIB and III, respectively. T-stage for node-negative patients (stage IA, IB, IIA only differ in T-stage) was neither predictive for survival in the 7th edition (log-rank $p = 0.96$), nor in the 8th edition (log-rank $p = 0.24$). The 8th edition N-stage was highly prognostic with 5-year survival rates of 35.6%, 20.1% and 10.9% for N0, N1 and N2 patients, respectively (log-rank $p < 0.0001$). When comparing prognostic accuracy, the C-statistic improved from 0.55 (95% confidence interval (CI), 0.52-0.57) in the 7th to 0.58 (95% CI, 0.55-0.60) in the 8th edition.

Conclusion: In this international cohort, the AJCC 8th edition of the TNM staging system for pancreatic cancer demonstrated a better distribution among different stages and an increased prognostic accuracy compared to the AJCC 7th edition. The new T-stage alone is still not predictive for survival, whereas the new N-stage is highly prognostic.

Product-Limit Survival Estimates

With Number of Subjects at Risk



9. RADIOLOGICAL FACTORS ASSOCIATED WITH MISSTAGING OF PANCREATIC DUCTAL ADENOCARCINOMA

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Background: A multidisciplinary approach to patients with pancreatic ductal adenocarcinoma (PDAC) is the standard of care and accurately staging is vital to developing a treatment plan. Unfortunately, >20% of patients evaluated at high volume centers are determined to have different stage of disease than initially believed. Factors contributing to the misstaging are poorly understood.

Methods: Patients presenting with PDAC to the Johns Hopkins Hospital (JHH) pancreatic multidisciplinary clinic (PMDC) from 2006-2014 who had scans performed at both an outside hospital (OH) and JHH within 30 days of each other were included. Two radiologists, blinded to reports of these scans, reviewed the OH and JHH scans. Factors contributing to PDAC patients' misstaging were identified.

Results: Of patients who presented at PMDC during the study period, 100 were included in the study. When OH scans were read by JHH radiologists, 36% had change in stage. New pancreas-protocol CT scans performed at JHH resulted in change in stage of 25% patients. For patients with a change in stage at JHH, a majority (80%) had more advanced disease than initially believed i.e. change from resectable, borderline or locally-advanced to metastatic disease. Only two (8.0%) patients had less disease than initially anticipated i.e. resectable disease at JHH after OSH evaluation showing more advanced disease. Blinded radiologist review revealed the causes of misstaging were: poor contrast timing (N=11,44.0%), low contrast enhancement (N=8,32.0%), lack of MPR/3D sections (N=2,8.0%), slice thickness (N=2, 8.0%), image noise (N=4,16.0%), disease progression (N=2,8.0%) and presumed radiologist experience (N=6,24.0%).

Conclusion: Approximately a quarter of patients with PDAC are misstaged on imaging due to multiple radiological factors. Attention to these factors can significantly reduce misstaging.

10. MARGIN STATUS AFTER PANCREATICO-DUODENECTOMY FOR CANCER: RESULTS OF A MULTICENTRIC PROSPECTIVE RANDOMIZED TRIAL

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Background: The method of pathological evaluation and the definition of minimum clearance significantly affect R1 rate after Pancreatico-Duodenectomy (PD) for cancer. The prognostic value of R1 resection is still controversial. The aims of this prospective multicentric randomized study were: a) to assess the impact of a standardized method of pathological evaluation in terms of R1 resection; b) to evaluate the prognostic impact of R status.

Methods: PD specimens were randomized to receive a standardized (guidelines of Royal College of Pathologists and 1 mm clearance) (group A) or a non-standardized (0 mm clearance) (group B) method of pathological evaluation. R1 rate and the impact of minimum clearance on R1 rate were evaluated. In patients affected by pancreatic cancer, the prognostic impact of R1 resection was also estimated. Given a 30% incidence of R1 resection with the non-standardized method, we expected that R1 rate would be observed at least in 60% of cases with a standardized method. Alpha is set at 0.05 and power at 80%. A sample size of 168 patients was calculated. To assess differences between proportions, X2 test was used. To assess risk modification of Local Recurrence (LR), a logistic regression model was used. Survival data were analyzed using Kaplan Meier analysis and log rank test.

Results: Between 2013-2015, 168 specimens were examined. PD was performed for pancreatic (123, 73.2%), ampullary (29, 17.3%) and distal common bile duct (16, 9.5%) cancer. R1 rate was 63.1% and 20.2% in group A and B ($p < 0.05$). When the same minimum clearance was applied, no differences between the two groups were found (0 mm: 26.1% and 20.2% for group A and B ($p > 0.05$); 1 mm: 63.1% and 54.8% for group A and B ($p > 0.05$)). Median follow-up was 33 months. LR was observed in 23.9% of cases. We didn't find any correlation between the risk of LR and: a) overall R1 rate; b) R1 rate for each group; c) R1 rate for each group adopting different clearances ($p = n.s.$). In pancreatic cancer cases, median Disease Free-Survival (DFS) and Overall Survival (OS) were 20 and 31 months (20 and 31 months for group A; 21 and 30 for group B; $p = n.s.$). Only if a 0 mm clearance was applied for group A, we found that R1 resection significantly affected OS and DFS (log-rank test $X^2(1) = 5.67$ and 5.68 , respectively; $p < 0.05$).

Conclusion: The standardized method of pathological evaluation and the 1 mm clearance significantly affects R1 resection rate after PD for cancer. Independently from adopted clearance, R1 resection rate is not significantly associated with an increased risk of LR. Finally, in pancreatic cancer cases, R1 resection significantly affects prognosis only if the standardized method and 0 mm clearance is adopted. A standardized method of pathological evaluation and 0 mm clearance should be adopted for a better evaluation of R1 resection rate after PD for cancer.

11. OUTCOMES AND RISK SCORE FOR DISTAL PANCREATECTOMY WITH CELIAC AXIS RESECTION (DP-CAR SCORE): AN INTERNATIONAL MULTICENTER ANALYSIS

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Background: Distal pancreatectomy with celiac axis resection (DP-CAR) is performed in selected patients with pancreatic cancer involving the celiac axis. However, a recent multicenter European study reported a 16% 90-day mortality. We constructed a risk score to predict 90-day mortality and assessed oncological outcomes.

Methods: Retrospective, multicenter study in patients undergoing DP-CAR at 20 European centers (model design; 2000-2016) and three very-high volume international centers in the USA and Japan (model validation; 2004-2017). We used the area-under-receiver-operator-curve (AUC) and calibration plots for validation of the 90-day mortality risk model. Secondary outcomes assessed included oncological outcomes such as resection margin status, (neo)adjuvant therapy use and survival.

Results: Among 191 DP-CAR patients, 90-day mortality was 5.5% (95CI: 2.2-11%) in 5 high-volume (≥ 1 DP-CAR/year) and 18% (95CI: 9-30%) in 18 low-volume DP-CAR centers ($P=0.020$). A risk score with age, sex, BMI, ASA, multivisceral resection, open versus minimally invasive surgery, and low versus high-volume center performed well in both, the design and validation cohort (AUC 0.79 versus 0.74, P value = 0.642) and calibration was adequate after adjustment. In 174 patients with pancreatic cancer, the R0 resection rate was 60%, neoadjuvant and adjuvant therapy was used in 69% and 67% of patients, and median overall survival was 19 (95CI 15-25) months.

Conclusion: DP-CAR is associated with acceptable 90-day mortality and survival in high-volume DP-CAR centers. We proposed a 90-day mortality risk score, with annual DP-CAR volume as dominant predictor, to improve patient selection and outcomes.

12. LEFT-SIDED PORTAL HYPERTENSION AFTER PANCREATODUODENECTOMY WITH RESECTION OF SUPERIOR MESENTERIC-PORTAL VEIN CONFLUENCE AND DIVISION OF SPLENIC VEIN: IMPACT OF COMBINED RESECTION OR LIGATION OF SPLENIC ARTERY

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Background: In pancreaticoduodenectomy (PD) with resection of portal vein (PV) /superior mesenteric vein (SMV) confluence, the splenic vein (SV) division sometimes causes left-sided portal hypertension (LPH), resulting in varices developing thrombocytopenia and splenomegaly. We previously reported that the concomitant division of SV and splenic artery (SA), so called PD-SAR (PD with Splenic Artery Resection), attenuated LPH in PD with resection of PV / SMV confluence (World J Surg 2017). Thereafter we have developed PD with SA ligation (PD-SAL) for the patients who underwent PD with resection of PV/SMV confluence and division of SV.

Methods: For pancreatic ductal adenocarcinoma (PDAC) involving PV/SMV, we underwent PD with resection of PV/SMV confluence as well as SV (PD-SVR) after chemoradiotherapy (CRT). When the SV or IMV was involved, they were divided and not reconstructed. Since June 2015, we had performed PD-SAL instead of PD-SVR. When the tumor involvement of SA as well as PV/SMV was identified, PD-SAR was employed.

From February 2005 to September 2017, 109 PDAC patients underwent PD with resection of PV/SMV following CRT. Twenty four patients were excluded from this study, owing to inadequate follow-up and simultaneous splenectomy. The remaining 85 patients were divided into three groups: PD-SVR (n=58), PD-SAR (n=16), and PD-SAL (n=11). We evaluated the effect of PD-SAL to attenuate LPH in patients who undergo PD with resection of PV/SMV confluence. LPH was evaluated by analyzing the frequency of developed varices and variceal bleeding, and postoperative platelet counts ratio and spleen volume ratio compared to preoperative data at 3 months (M) after PD.

Results: The backgrounds and surgical outcomes among three groups did not significantly differed except for the rates of locally advanced (LA) PDAC according to IAP international consensus 2017 (Pancreatology 2017) (17.3% in PD-SVR, 62.5% in PD-SAR and 18.2% in PD-SAL, $p=0.025$) and R0 resection (93.1%, 62.5% and 100%, respectively, $p=0.004$). In PD-SAR and PD-SAL, there were no complications related to SA resection or ligation including splenic infarction, insufficiency of blood flow into pancreatic tail or remnant stomach, and aneurysm of the SA. Incidence of variceal development evaluated by CT was 67.2% in PD-SVR, 31.1% in PD-SAR, and 36.4% in PD-SAL, respectively ($p=0.029$). Variceal bleeding was experienced in 4 patients, all of whom received PD-SVR (6.8%). Platelet counts ratio at 3M post operatively was lowest in PD-SVR (0.77), followed by PD-SAL (0.90) and PD-SAR (1.20) (PD-SVR vs. PD-SAR, $p=0.032$). Spleen volume ratio at 3M postoperatively was highest in PD-SVR (1.33), followed by PD-SAL (1.14) and PD-SAR (0.76) (PD-SVR vs. PD-SAR, $p<0.001$).

Conclusion: PD with resection of PV/SMV confluence and division of SV caused LPH, which increases the risk of variceal bleeding and hypersplenism. The concomitant resection or ligation of SA can attenuate LPH.

13. SPLENECTOMY DURING DISTAL PANCREATECTOMY: WHAT ARE WE REALLY DOING?

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Background: The performance of a splenectomy is one of the few major decision points in distal pancreatectomy (DP). Although this represents a particularly common clinical scenario, evidence regarding splenectomy and splenic preservation (SP) during DP is nebulous. The aim of this study was to analyze surgeons' opinions and preferred strategies regarding splenectomy during DP, and to identify possible contributors of variability in practice.

Methods: A survey assessing surgeons' beliefs and practices for splenectomy during DP was distributed worldwide, in 8 native-language translations, through 56 surgical societies including the Pancreas Club. The participants' answers were related to their demographic characteristics (age, region of practice), background (fellowship training, type of fellowship, scope of practice), and indicators of experience (annual/career volume of DPs).

Results: 797 surgeons from 68 nations responded (median age=47; years of experience=14; fellowship-trained=62%). Most of them are HPB surgeons (61%), followed by general surgeons (16%) and surgical oncologists (12%), while only 7% practices pancreatic surgery exclusively. Their median annual and career volumes are 6 and 46 DPs, respectively. Respondents are conflicted regarding the benefit of SP during DP, with 35% considering it not or only marginally beneficial, and around 60% judging it moderately to markedly advantageous. SP is rarely applied when operating for malignancy, while a wide variety of approaches are employed for non-malignant disease. Among surgeons performing SP, conservation of the splenic vessels is the most common approach (82.5%), while the Warshaw technique is preferred only 17.5% of the time. In the case of DP with splenectomy, surgeons overwhelmingly agree on the need for perioperative immunization (92%). However, while *S.Pneumoniae* vaccination is almost always administered, those against *H.Influenzae* and *N.Meningitidis* are more rarely chosen. Moreover, there is a broad heterogeneity of behaviors regarding the preferred timing for immunization (most frequent= > 2weeks before surgery). Finally, there is no agreement on the need for anti-platelet therapy after splenectomy, and different cut-off values of platelets are used. Surgeons' opinions and strategies are to some extent related to their age, scope of practice, and experience, but the strongest driver of variability is geographic origin (Table). Conversely, fellowship training appears to have only marginal influence on practice.

Conclusion: There is wide heterogeneity in beliefs and practices regarding splenectomy during DP, which appears mainly influenced by the surgeon's region of practice. These results suggest that current behaviors are mostly driven by cultural factors and perpetuated dogmas, rather than scientific evidence, which remains largely inadequate. These findings indicate focused areas for further research and improvement.

Table. Surgeons' opinions and preferred strategies regarding splenectomy during distal pancreatectomy for all respondents (n=797) and stratified based on the region of practice (n=721 due to some surgeons not indicating their geographical area).

Variable	All Respondents (n=797)	Differences based on region of practice (n=721)				p-value
		North America	South/Central America	Europe/Africa/Middle East	Asia/Oceania	
Surgeons, n (%)	797 (100)	182 (25.2)	109 (15.1)	195 (27.0)	235 (32.6)	-
Do you believe that spleen-preservation is beneficial?						<0.001
No	131 (16.5)	69 (37.9)	16 (14.7)	13 (6.7)	19 (8.1)	
Marginally	153 (19.2)	45 (24.7)	12 (11.0)	38 (19.6)	37 (15.8)	
Somewhat	283 (35.6)	51 (28.0)	29 (26.6)	77 (39.7)	102 (43.6)	
Very much	192 (24.2)	10 (5.5)	46 (42.2)	59 (30.4)	65 (27.8)	
I don't know	36 (4.5)	7 (3.8)	6 (5.5)	7 (3.6)	11 (4.7)	
Do you use spleen-preservation for malignant disease?						0.011
Never	632 (80.1)	155 (85.2)	81 (75.7)	162 (83.5)	179 (76.8)	
Occasionally 1-25%	108 (13.6)	17 (9.3)	15 (14.0)	23 (11.9)	42 (18.0)	
Sometimes 26-75%	37 (4.7)	9 (4.9)	6 (5.6)	7 (3.6)	10 (4.3)	
Frequently 76-99%	7 (0.9)	0	4 (3.7)	1 (0.5)	0	
Always	5 (0.6)	1 (0.5)	1 (0.9)	1 (0.5)	2 (0.9)	
Do you use spleen-preservation for non-malignant disease?						<0.001
Never						
Occasionally 1-25%	51 (6.5)	21 (11.7)	5 (4.7)	6 (3.1)	14 (6.1)	
Sometimes 26-75%	207 (26.5)	77 (42.8)	29 (27.1)	34 (17.8)	46 (19.9)	
Frequently 76-99%	274 (35.1)	57 (31.7)	29 (27.1)	69 (36.1)	100 (43.3)	
Always	197 (25.2)	24 (13.3)	29 (27.1)	67 (35.1)	57 (24.7)	
I do not perform it	52 (6.7)	1 (0.6)	15 (14.0)	15 (7.9)	14 (6.1)	
Which is your preferred technique for splenic preservation?						<0.001
Splenic vessel preservation	609 (76.6)	110 (60.8)	88 (81.5)	159 (81.5)	190 (80.9)	
Warshaw technique	129 (16.2)	46 (25.4)	14 (13.0)	30 (15.4)	32 (13.6)	
I do not perform it	57 (7.2)	25 (13.8)	6 (5.6)	6 (3.1)	13 (5.5)	
In the case of DP with splenectomy, do you recommend perioperative immunization?						0.001
No	61 (7.7)	4 (2.2)	7 (6.4)	19 (9.7)	30 (12.8)	
Yes	736 (92.3)	178 (97.8)	102 (93.6)	176 (90.3)	205 (87.2)	
Which vaccinations do you recommend? *						0.172
Streptococcus Pneumoniae	719 (97.7)	177 (99.4)	100 (98.0)	169 (96.0)	198 (96.6)	
Haemophilus Influenzae	560 (76.1)	170 (95.5)	81 (79.4)	148 (84.1)	96 (46.8)	<0.001
Neisseria Meningitidis	490 (66.6)	173 (97.2)	60 (58.8)	114 (64.8)	80 (39.0)	<0.001
Seasonal anti-flu	255 (34.6)	77 (43.3)	23 (22.5)	69 (39.2)	51 (24.9)	<0.001
When do you immunize the patient? *						<0.001
At least 2 weeks before surgery	412 (56.1)	129 (72.5)	67 (65.7)	77 (43.8)	92 (45.3)	
Within 2 weeks before surgery	72 (9.8)	15 (8.4)	15 (14.7)	12 (6.8)	25 (12.3)	
Post-operatively in the hospital	77 (10.5)	19 (10.7)	8 (7.8)	20 (11.4)	24 (11.8)	
After discharge < 2 weeks from the operation	58 (7.9)	4 (2.2)	8 (7.8)	24 (13.6)	14 (6.9)	
After discharge ≥ 2 weeks from the operation	115 (15.7)	11 (6.2)	4 (3.9)	43 (24.4)	48 (23.6)	
Do you believe that future boosters are necessary? *						<0.001
No	149 (20.3)	29 (16.3)	34 (33.3)	33 (18.8)	41 (20.1)	
Yes, every year	51 (6.9)	8 (4.5)	16 (15.7)	12 (6.8)	10 (4.9)	
Yes, every 5 years	332 (45.2)	86 (48.3)	29 (28.4)	80 (45.5)	103 (50.5)	
Yes, every 10 years	47 (6.4)	14 (7.9)	7 (6.9)	11 (6.3)	7 (3.4)	
I don't know	155 (21.1)	41 (23.0)	16 (15.7)	40 (22.7)	43 (21.1)	
In the case of DP with splenectomy do you prescribe antiplatelet therapy?						<0.001
No never	227 (28.5)	41 (22.5)	59 (54.1)	55 (28.2)	57 (24.3)	
Yes, for platelets > 500.000/ µl	116 (14.6)	11 (6.0)	26 (23.9)	11 (5.6)	15 (6.4)	
Yes, for platelets > 750.000/ µl	104 (13.0)	9 (4.9)	2 (1.8)	28 (14.4)	46 (19.6)	
Yes, for platelets > 1000.000/ µl	309 (38.8)	119 (65.4)	12 (11.0)	31 (15.9)	47 (20.0)	
Yes, in every case	41 (5.1)	2 (1.1)	10 (9.2)	70 (35.9)	70 (29.8)	

*Only for surgeons who recommend perioperative immunization

14. ANALYSIS OF ABSTRACTS PRESENTED AT THE PANCREAS CLUB ANNUAL MEETING AND THEIR PROCEEDING TO FULL PUBLICATION

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Background: The Pancreas Club annual meeting program is drawn entirely from a call for abstracts. This study evaluated the conversion rate to full publications and the post-publication impact of abstracts presented over a three-year period.

Methods: All abstracts presented between 2011 and 2013 were retrieved. Cross-referencing of title, keywords, and authors was performed using PubMed database. The resultant full-text publications were assessed with the index abstracts for content matching. Information was collected on authors' geographical origin and lag time to publication. Furthermore, bibliometric data, including the journal impact factor (IF) and the number of citations garnered as of October 2017, were recorded.

Results: 497 abstracts were presented during the study period. Most came from America (66.6%). 150 abstracts (30.2%) were presented in oral form, while 347 (69.8%) as posters. American abstracts were more likely to be presented orally compared with non-American ones (33.1% vs 18.0% $p < 0.001$). The bulk of abstracts were clinical (73.6%), however basic science abstracts were most frequently presented as oral (38.6% vs 21.0%, $p < 0.001$). Of the 497 abstracts presented, 315 (63.4%) proceeded to full publication. There was no difference in the proportion of works that were eventually published when stratifying by clinical vs basic science ($p = 0.756$) and by geographical region ($p = 0.799$). Oral abstracts were more likely to progress to full publication compared with posters (70.6% vs 60.2%, $p = 0.002$). Among the published papers, 11 (3.5%) appeared in journals without IF; these had all been presented as posters. The Journal of Gastrointestinal Surgery was the main outlet of research presented at the meetings (50 full-text publications, 15.9%). 25 works (7.9%) had already been published at the time of meeting presentation. For the remaining 290 manuscripts, the median time to publication was 16.2 months, with no difference between oral and poster presentations ($p = 0.85$). There was no difference in the median journal IF when stratifying by geographical origin ($p = 0.664$). Yet, the median IF was significantly greater in basic science papers (3.71 vs 2.91, $p = 0.0001$), and in works that had been presented orally (3.56 vs 2.91, $p = 0.001$). There was no difference in the median number of citations when stratifying by geographical origin ($p = 0.192$) and by clinical versus basic science ($p = 0.378$). Conversely, the median number of citations was significantly different according to the type of presentation (28 oral vs 19 poster, $p = 0.001$).

Conclusion: More than 60% of abstracts presented at the Pancreas Club between 2011 and 2013 were published in full-text. Oral abstracts were most likely to proceed to full publication in comparison with posters, and generally reached greater post-publication impact. The present results suggest that scientific gatekeeping by the program committee was effective at recognizing and promoting quality.

15. FACTORS PREDICTING SURVIVAL AFTER PANCREATECTOMY WITH ARTERIAL RESECTION FOR PANCREATIC DUCTAL ADENOCARCINOMA

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Background: The combination of high postoperative mortality and poor survival have limited the role of pancreatectomy with arterial resection (P-Ar) in the treatment of pancreatic ductal adenocarcinoma (PDAC). The recent availability of effective oncologic therapies is promoting a reassessment of P-Ar. We herein present the results of an analysis aimed at identifying the factors associated with overall survival (OS) and disease specific survival (DSS) in P-Ar for PDAC.

Methods: Using a prospectively maintained database we performed a retrospective cross-sectional study of patients who underwent P-Ar for PDAC between January 1993 and July 2017. OS and DSS were calculated using Kaplan-Meier curves and Log-rank test. Post-operative mortality was censored in survival analysis. Univariate proportional hazards regression and multivariate proportional hazards model analyses were used to identify the prognostic factors.

Results: Eighty-six patients received a P-Ar for PDAC. Ninety-day mortality was 8.6% (10/86). The 76 patients who survived P-Ar had a mean age of 63.3 ± 9.7 years, a mean BMI of 23.4 ± 2.6 , a median ASA score of 2 (2-3), and included 33 males (43.4%). P-Ar consisted of a total pancreatectomy in 44 patients (71.1%), of a distal pancreatectomy in 15 patients (19.7%), and of a pancreaticoduodenectomy in 7 patients (9.2%). P-Ar included resection of an isolated arterial segment in 18 patients (23.4%), and of at least one arterial and one venous segment in the remaining 58 patients (76.3%). The superior mesenteric artery (SMA) and the hepatic artery/celiac axis were resected in 28 (36.8%) and 58 (76.3%) patients, respectively. Median OS and DSS were 14.2 (9.8-26.3) and 16.7 (10.4-31) months, respectively. Prognostic factors identified in the univariate analysis are reported in table 1. For OS, multivariate analysis confirmed the prognostic relevance of completion of adjuvant therapy (HR= 0.23, $p=0.01^*$) and Ca 125 level (HR=1.04, $p=0.01^*$) (Model OS, -Log-likelihood= 6.94, $p=0.001^*$). For DSS, multivariate analysis showed the prognostic relevance of age (HR= 0.80, $p<0.001^*$), neoadjuvant therapy (HR= 0.01, $p<0.001^*$), Ca 15.3 level (HR= 1.31, $p<0.001^*$), completion of adjuvant therapy (HR= 0.08, $p=0.001^*$), Ca 125 level (HR=1.06, $p=0.001^*$), resection of SMA (HR= 0.09, $p=0.002^*$), and grade C post-pancreatectomy haemorrhage (HR=641.4, $p=0.003^*$) (Model DSS, -Log-likelihood=19.1, $p<0.001^*$).

Conclusion: We have identified several prognostic factors in P-Ar for PDAC. Interestingly, some of these parameters are not related to the biology of the individual PDAC but rather to the quality of care (e.g. lack of grade C post-pancreatectomy haemorrhage, and completion of adjuvant therapy). Identification of referral centers, resulting in higher volumes per Institution, could result in improved survival.

Table 1 – Univariate proportional hazards regression

	-Log-likelihood	p (model)	β	p (β)	HR (95% CI)
For Overall Survival					
COPD	2.13	0.04*	1.13	0.04*	3.10 (1.07-7.16)
Smoke	2.63	0.02*	0.83	0.02*	2.29 (1.13-4.30)
Neoadjuvant chemotherapy	3.06	0.01*	-0.64	0.01*	0.52 (0.30-0.87)
CEA level	2.94	0.02*	0.05	0.02*	1.05 (1.01-1.10)
Ca 15.3 level	4.35	0.003*	0.04	0.003*	1.04 (1.01-1.06)
Ca 125 level	4.42	0.003*	0.02	0.03*	1.01 (1.01-1.02)
HA/CA resection	2.27	0.03*	0.68	0.03*	1.98 (1.05-4.16)
SMA resection	1.30	0.10	-0.45	0.10	0.64 (0.36-1.09)
Colic resection	2.25	0.03*	1.17	0.03*	3.25 (1.10-7.64)
Post-operative course without complications	1.38	0.09	-0.46	0.09	0.63 (0.34-1.08)
Grade C post-pancreatectomy haemorrhage	1.83	0.05*	1.04	0.05*	2.82 (0.97-6.53)
Number of positive lymph nodes	2.00	0.05*	0.05	0.05*	1.05 (1.00-1.10)
Lymph nodes ratio	3.53	0.008*	3.58	0.008*	35.8 (2.82-298.67)
LODDS	2.28	0.03*	9.57	0.03*	1.76 (1.05-2.90)
Completion of adjuvant therapy	5.24	0.001*	-1.61	0.001*	0.20 (0.007-0.53)
For Disease Specific Survival					
Age	2.72	0.02*	0.65	0.02*	1.92 (1.11-3.34)
COPD	2.71	0.02*	1.31	0.02*	3.71 (1.26-8.69)
Smoke	3.74	0.006*	1.02	0.006*	2.79 (1.36-5.36)
Neoadjuvant chemotherapy	4.32	0.003*	-0.84	0.003*	0.43 (0.23-0.76)
CEA level	2.86	0.02*	0.06	0.02*	1.06 (1.01-1.10)
Ca 15.3 level	2.41	0.03*	0.03	0.03*	1.03 (1.00-1.06)
Ca 125 level	1.97	0.05*	0.01	0.05*	1.01 (1.00-1.02)
Lymphocytes-to-monocytes ratio	1.36	0.10	-0.22	0.10	0.80 (0.61-1.04)
HA/CA resection	5.64	0.008*	1.32	0.008*	3.77 (1.65-10.9)
SMA resection	2.62	0.02*	-0.69	0.02*	0.49 (0.25-0.90)
Colic resection	1.68	0.06	1.13	0.06	3.10 (0.91-7.97)
Post-operative course without complications	1.62	0.07	-0.55	0.07	0.57 (0.29-1.04)
Grade C post-pancreatectomy haemorrhage	2.37	0.03*	1.21	0.03*	3.36 (1.15-7.90)
Lymph nodes ratio	1.61	0.07	2.81	0.07	16.67 (0.75-200.9)
LODDS	1.79	0.05	0.54	0.05	1.72 (0.98-2.97)
Completion of adjuvant therapy	4.22	0.004*	-1.47	0.004*	0.23 (0.08-0.62)

COPD= Chronic Obstructive Pulmonary Disease; CEA= Carcinoembryonic antigen; Ca 15.3= Cancer antigen 15.3; Ca 125= Cancer antigen 125; HA/CA= hepatic artery/celiac axis; SMA= superior mesenteric artery; LODDS= log odds of positive lymph nodes

16. PROSPECTIVE OBSERVATIONAL ANALYSIS OF NEOADJUVANT THERAPY FOR LOCALIZED PANCREATIC CANCER: A THREE-YEAR, SINGLE-CENTER EXPERIENCE ON 769 PATIENTS

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Background: Neoadjuvant therapy (NAT) is gaining momentum in the treatment of localized pancreatic adenocarcinoma (L-PDAC), based on promising survival outcomes reported in those patients who were eventually resected. However, there is little information on patients who receive NAT with intent for later pancreatectomy, but did not ultimately proceed to surgery. The aim of this observational study was to evaluate the clinical applicability and results of NAT in an intention-to-treat fashion.

Methods: Patients with L-PDAC submitted to NAT from 2013 through 2015 were included in the analysis. Exclusion criteria were metastatic disease and upfront resection. The initial resectability status was classified according to the NCCN guidelines. Data on initiation, type and completion of NAT were captured, as well as the rate of surgical exploration and resection. The primary endpoint was the disease-specific survival (DSS) following NAT. Sub-analysis were performed stratifying by resectability status at diagnosis and by performance of successful resection.

Results: The study population consisted of 769 patients, of whom 11.7% were resectable (R), 35.2% borderline resectable (BR) and 53.1% locally advanced (LA) at the diagnosis. 8.5% of patients were lost to follow-up. Remarkably, 7.9% of patients were never started on NAT, due to ineligibility after oncologic screening or rapid clinical deterioration. When NAT was initiated, its completion rate was 72.1%. Of note, 33% of patients received a second-line therapy. The most common NAT protocols were FOLFIRINOX (50%), Gemcitabine/Nab-Paclitaxel (31%), Gemcitabine (31%) and Gemcitabine-Oxaliplatin (15%). 22.4% of patients received additional radiation therapy. Overall, 23.7% of patients underwent surgical exploration after NAT, with significant differences according to the NCCN class at the time of diagnosis (28.6% vs 30.7% vs 17% for R, BR and LA patients respectively, $p < 0.001$). Only 15.3% of patients were ultimately resected (22.0% versus 23.9% vs 8.4% for R, BR and LA patients, $p < 0.001$). The R0 resection rate was 62%. The median DSS of the entire cohort was 13.2 months (95% CI 12.2-14.2). There was no difference between R and BR PDAC, whereas the DSS was shorter in LA patients (14.2 vs 14.3 vs 12.3 months, $p = 0.006$). When limiting the analysis to resected patients, the median DSS was 35 months (95% CI 30.1-38.4), with no significant differences when stratifying by resectability status prior to NAT.

Conclusion: This is the first intention-to-treat analysis of NAT in L-PDAC, providing a comprehensive picture of its real clinical impact. A substantial amount of patients will not complete the treatment schedule, and will never qualify for surgical exploration, with a disappointing overall resection rate of 15.3%. Significant differences in survival are identifiable based on resectability status at the time of diagnosis; however these disappear when resection is successfully undertaken.

17. A PRE-OPERATIVE MOLECULAR PROGNOSTIC NOMOGRAM FOR RESECTABLE PANCREATIC CANCER

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Background: About 80% of patients with pancreatic cancer (PC) succumb to the disease despite curative resection, many of whom recur within 6 months of surgery. This suggests current staging is inadequate and there is a clear need to better define the biology and clinical behaviour of PC prior to significant intervention. This study aimed to evaluate the potential clinical utility of biologically relevant molecules as prognostic factors in resected PC to improve current preoperative staging accuracy and inform treatment decisions.

Methods: We assessed the relationship of aberrant expression of two pro-metastatic calcium-binding proteins, S100A2 and S100A4 with disease-specific survival in three independent cohorts of patients who underwent operative resection for PC (total patients = 1184). A preoperative nomogram using pre-operatively assessable variables including biomarkers was compared to traditional prognostic variables and a postoperative nomogram.

Results: High S100A2 and S100A4 expression were independent poor prognostic factors ($n = 514$; HR = 1.32, 95% CI = 1.03 - 1.69, $P = 0.028$ and HR = 1.63, 95% CI = 1.29 - 2.05, $P < 0.001$ respectively). These results were further validated in two independent cohorts (Glasgow Royal Infirmary, $n = 198$, and University of Dresden, $n = 468$). Aberrant expression of S100A2/A4 protein stratified the cohorts into three distinct prognostic groups. High S100A2/A4 expression associated with the poor prognostic Squamous (also known as Basal or Quasi-Mesenchymal) molecular subtype of PC. A preoperative nomogram using only variables that could be measured preoperatively, predicted survival as accurately as nomograms derived using post-operative variables. A proof-of-principle study demonstrated that biomarker expression can be reliably assessed in preoperative EUS-FNA samples ($n = 28$).

Conclusion: Aberrant S100A4 and S100A2 expression stratifies patients with resected PC into distinct prognostic groups and improves the accuracy of a prognostic nomogram using variables that can be determined pre-operatively. Biomarker assessment potentially enables accurate preoperative prognostication and has the potential to improve patient selection for surgery.

18. SENSITIZING PANCREATIC CANCER CELLS BY UTILIZING TARGETED SIHUR NANOTHERAPY

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Background: HuR is an RNA binding protein involved in a coordinated response to cellular stressors. Upon insults, such as chemotherapy or radiation treatment, HuR translocates from the nucleus to the cytoplasm where it binds the 3' UTR of target mRNA's. HuR's interaction with target mRNA's leads to the upregulation of pro-survival target genes and ultimately treatment resistance. This is particularly relevant in the case of pancreatic ductal adenocarcinoma (PDA). PDA is highly resistant to standard chemotherapy such as FOLFIRINOX or gemcitabine/nab-paclitaxel. It has been previously shown that CRISPR-mediated deletion of HuR increases sensitivity to a variety of drugs including PARP inhibitor olaparib (Lynparza) over 20-fold in vitro, and using a doxycycline-inducible HuR depletion (shHuR) combined with olaparib treatment resulted in a 9.3-fold ($p < 0.001$) decrease in tumor volume in vivo. The aim of our current study is to target HuR directly using nanoparticle delivery siRNA against HuR (siHuR) to determine efficacy of this preclinical model.

Methods: 3DNA (Genisphere, LLC) is a 60nm nanoparticle composed of a sphere of crosslinked DNA that can be targeted using moieties that are overexpressed on the surface of PDA cells EGFR, folic acid receptor, and transferrin receptor. These receptors were stained for on a human PDA microarray (TMA) to quantify their prevalence. In vitro testing with siHuR was done in Mia PaCa-2 and HS766T pancreatic cancer cell lines, and RNA quantification was performed via real time PCR (qPCR). In vivo, athymic female nude mice were injected with 4 million Mia PaCa-2 cells per flank, and randomized to treatment arms when tumors reached 100mm³. Mice were then treated intraperitoneally (IP) twice weekly with either siHuR (3ug siRNA) or siControl 3DNA against each targeting moieties.

Results: Staining human TMA showed 79% of patient tumor samples (n=70) were positive for active cytoplasmic HuR, with little to no cytoplasmic localization in normal tissue. EGFR was overexpressed in 42% of tumors while transferrin and folic acid receptors were overexpressed in 100% of tumors. In vitro, modified siHuR transfection (modified to escape systemic RNAses) was shown to decrease both RNA and protein levels of HuR in Mia PaCa-2 and HS766T cell lines along with decreased RNA expression of other HuR targets including DCK, IDH1 and PIM1. In vivo, treatment of siHuR was found to be safe and effective at extending life in a xenograft model by Kaplan Meier analysis ($p=0.01$).

Conclusion: In conclusion, HuR inhibition can sensitize PDA cells to chemotherapy and targeted therapies in vitro and 3DNA delivery of siHuR and is safe and effective in vivo. We are currently investigating in vivo combined treatments with modified siHuR 3DNA with olaparib or oxaliplatin, to further improve drug efficacy and provide a new treatment option for patients with pancreatic cancer.

19. EXPLORING THE MICROENVIRONMENT OF THE PORTAL VENOUS CIRCULATION IN PANCREATIC CANCER: CIRCULATING TUMOR CELL/IMMUNE CELL INTERACTIONS

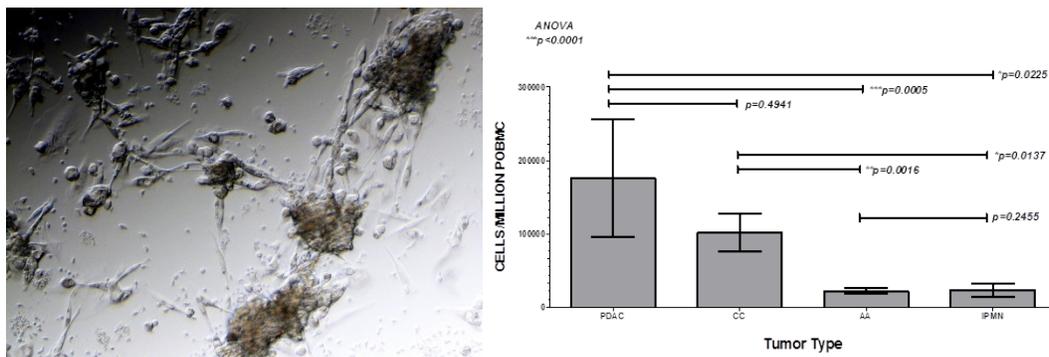
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Background: Complete surgical resection is the best option for curative treatment of pancreatic ductal adenocarcinoma (PDAC). We postulate that metastatic dispersion of tumor cells via the portal venous system supports tumor progression favored by an immune-suppressed environment. Our recent studies point to the presence of portal circulating tumor cells (CTC) that express active mutated K-RAS mRNA, as opposed to CTC detected in peripheral blood.

Methods: To characterize the portal blood CTC metastatic potential, we have developed an ex vivo mixed cell reaction (MCR) culture platform using fluorescence-activated cell sorting (FACS) of portal blood collected during pancreaticoduodenectomy (n=37) for various peri-ampullary pathologies, (PDAC=10; ampullary adenocarcinoma (AA)=13; distal cholangiocarcinoma (CC)=6; IPMN=6; non-malignant pancreatitis=2) The MCR reconstituted the CTC interaction with additional circulating cell types that included immune cells (T cells, macrophages, dendritic cells) and stroma-producing fibroblasts, to allow for molecular analyses of these interactions.

Results: In the MCR, PDAC and cholangiocarcinoma CTC spontaneously formed clusters and recruited additional cells to form spheroid-like foci after 5-7 days in culture. Through FACS-selective cell population depletion and reconstitution experiments, we found that CTC cluster formation incorporated multiple cell types but were exclusively dependent on the presence of CTC (CD44+CD147+EPCAM+) and a subpopulation of CD105+ fibroblasts carrying myeloid lineage markers (CD14+) for their formation. During the first 24 to 48hr, PDAC, AA, and CC patient CTC were all highly proliferative (mean 2.6 hr/ cell cycle, 65% growth, $\pm 17\%$) and resistant to apoptosis (mean 37%, $\pm 24\%$) compared to IPMN and non-malignant patient cultures ($p=0.0006$), Figure 1. PDAC CTC proliferation and resistance to T cell cytotoxicity were decreased by pre-operative chemotherapy treatment ($p=0.007$, $p=0.04$, respectively), and by ex vivo treatment with indomethacin ($p=0.01$). In PDAC and CC, cluster formation promoted CTC survival, growth, and fibroblast differentiation. FACS depletion of CTC or myeloid fibroblast cells eliminated cluster network formation, and re-introduction of these depleted cell populations reconstituted this ability.

Conclusion: Following pancreaticoduodenectomy, the portal venous blood system harbors remnant CTC that spontaneously cluster with immune cells and fibroblasts within an immunosuppressive microenvironment conducive to their survival and potential dissemination. Using this individualized ex vivo platform, we have been able to testbed drug candidates for potential intra-portal treatment options, while evaluating the residual tumor cell burden, and assessing the immune responsiveness of patient-derived CTC, within days of surgical resection.



20. COMBINED CIRCULATING TUMOR DNA AND PROTEIN BIOMARKER-BASED LIQUID BIOPSY FOR THE EARLIER DETECTION OF PANCREATIC CANCERS

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Background: The earlier diagnosis of cancer is one of the keys to reducing cancer deaths in the future. Here we describe our efforts to develop a noninvasive blood test for the detection of pancreatic ductal adenocarcinoma.

Methods: We combined blood tests for KRAS gene mutations with carefully thresholded protein biomarkers to determine whether the combination of these markers was superior to any single marker. The cohort tested included 221 patients with resectable pancreatic ductal adenocarcinomas and 182 control patients without known cancer.

Results: KRAS mutations were detected in the plasma of 66 patients (30%), and every mutation found in the plasma was identical to that subsequently found in the patient's primary tumor (100% concordance). The use of KRAS in conjunction with four thresholded protein biomarkers increased the sensitivity to 64%. Only one of the 182 plasma samples from the control cohort was positive for any of the DNA or protein biomarkers (99.5% specificity).

Conclusion: This combinatorial approach may prove useful for the earlier detection of many cancer types.

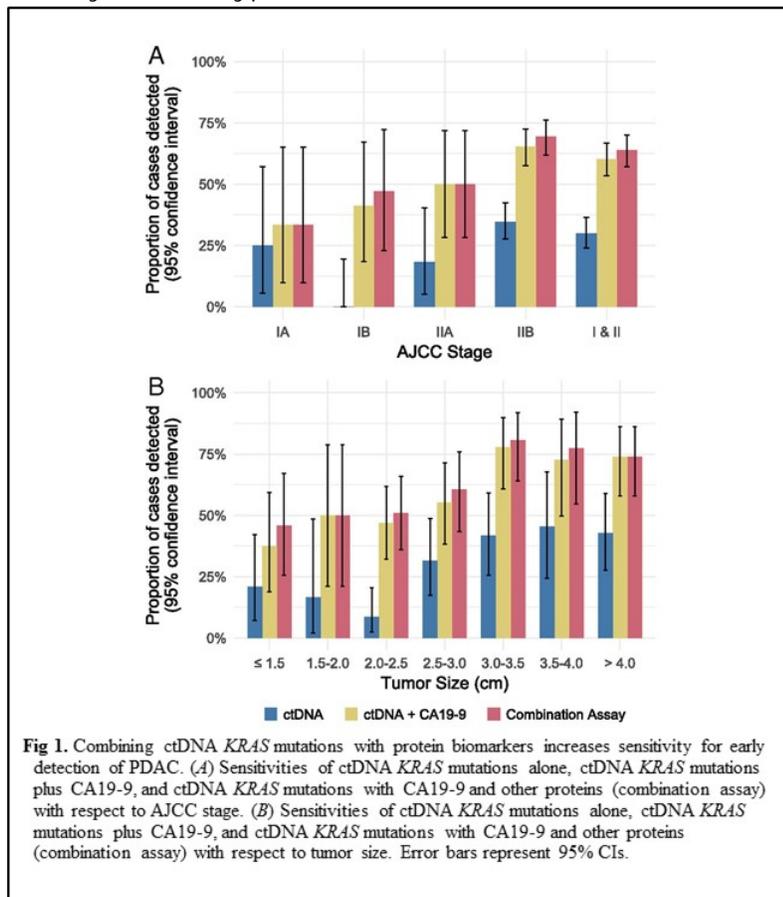


Fig 1. Combining ctDNA *KRAS* mutations with protein biomarkers increases sensitivity for early detection of PDAC. (A) Sensitivities of ctDNA *KRAS* mutations alone, ctDNA *KRAS* mutations plus CA19-9, and ctDNA *KRAS* mutations with CA19-9 and other proteins (combination assay) with respect to AJCC stage. (B) Sensitivities of ctDNA *KRAS* mutations alone, ctDNA *KRAS* mutations plus CA19-9, and ctDNA *KRAS* mutations with CA19-9 and other proteins (combination assay) with respect to tumor size. Error bars represent 95% CIs.

21. CIRCULATING MICRORNAS AS TREATMENT RESPONSE MARKERS OF SURGERY AND FOLFIRINOX IN PATIENTS WITH PANCREATIC CANCER

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Background: Predicting which patient with pancreatic ductal adenocarcinoma (PDAC) will respond to therapy is challenging and many patients will not benefit from treatment due to organ metastasis and chemotherapy resistance. More than half of treated patients will experience a grade 3 or 4 adverse event caused by toxicity of FOLFIRINOX chemotherapy. MicroRNAs (miRs) are short RNAs (~20 nucleotides) that control cellular pathways in both physiology and pathology by regulating mRNA stability and/or protein translation. Many of the distinct miRs expressed in different organs are shed into the circulation, and can serve as stable biomarkers of the presence of an altered physiologic state as well as malignant disease progression. Monitoring responses to therapy using changes in the expression patterns of circulating miRs could be useful in treatment decision making and prognostication of patients. Here we sought to establish circulating miR signatures indicative of PDAC recurrence after surgical tumor removal or FOLFIRINOX therapy.

Methods: Serum miRs were measured using the novel miR-specific IDEAL[®] miRNA qPCR assay (MiRXES). Conformational restricted miR specific reverse transcription primers efficiently hybridize to mature but not precursor forms of target miRs. Forward and reverse real-time qPCR primers confer further specificity and enable robust miR amplification. Peripheral venous blood was collected before and after therapy of 22 patients with PDAC that were treated by either Whipple surgery or the first cycle of FOLFIRINOX therapy. Five patients who underwent Whipple surgery for pancreatitis or benign intraductal papillary mucinous neoplasm (IPMN) served as controls for the surgical procedure. Up to 250 miRs were measured and analyzed for changes in miRs indicative of surgical PDAC removal and progression free survival (PFS) duration. Principal Component Analyses (PCA) were used to compare miR expression patterns in patients with different outcome after therapy.

Results: Whipple surgery resulted in 9 differentially expressed serum miRs which could distinguish PDAC patients with different PFS. A comparison with circulating miR patterns in patients who underwent comparable surgery for benign disease showed that these miR changes were not related to the procedure, but indicative of successful removal of cancer tissue. The impact of one FOLFIRINOX infusion on circulating miRs showed that 11 miRs may indicate distinct clinical response. The downregulation of four miRs after Whipple surgery and after FOLFIRINOX occurs only in patients with long PFS with either resectable or locally advanced PDAC. Three of four response miRs are also deregulated in LSL-Kraswt/G12D; LSL-Trp53wt/R175H; P48wt/Cre (KPC) transgenic mice with metastatic disease.

Conclusion: Circulating miRs may be used as biomarkers to indicate surgery and FOLFIRINOX responses in patients with PDAC, which is currently being validated.

22. PATTERNS OF BIOMARKER EXPRESSION PREDICT SURVIVAL AFTER RESECTION IN PANCREATIC CANCER: A RETROSPECTIVE COHORT STUDY AND CLUSTER ANALYSIS

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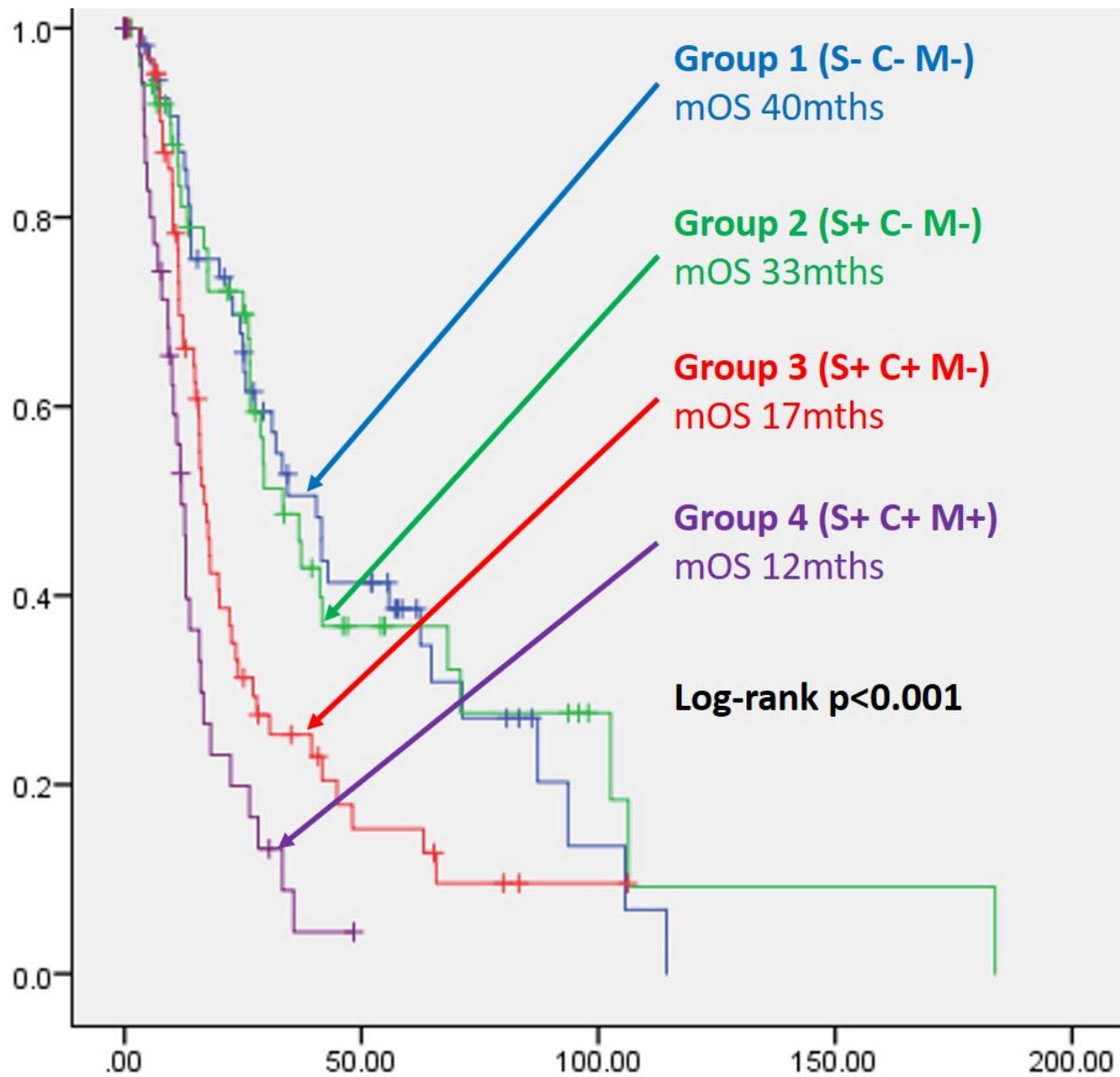
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Background: Up to 35% of patients undergoing surgical resection for pancreatic ductal adenocarcinoma (PDAC) succumb to recurrent disease within one year of surgery despite routine pre-operative staging and complete resection. We previously published a systematic review of tumour biomarkers with perioperative prognostic significance in PDAC, and shortlisted a panel of those reported with the highest level of evidence that could be immunohistochemically detected. These were p53, CDKN2A, Ca125, S100A4, FOXC1, EGFR, mesothelin, smad4, CD24, and UPAR. We aimed to determine whether simultaneous assessment of these proteins would reveal patterns of biomarker expression that could accurately stratify survival outcomes after PDAC resection.

Methods: Patients who underwent PDAC resection from 1996 to 2016 were included for analysis. Tissue microarrays of formalin fixed paraffin embedded pancreatic tumour specimens were constructed for all patients, stained by immunohistochemistry for all ten proteins, and scored for immunolabelling intensity and percentage of tumour cells stained. Survival analysis was undertaken by Kaplan-Meier method and difference in survival outcomes were assessed by log rank method and. Two-step cluster analysis was performed using biomarkers individually shown to be of prognostic significance to identify patterns of biomarker expression associated with different survival outcomes.

Results: 249 patients were included for analysis. Individual biomarker expression associated with shorter mOS included: S100A4 (18 vs 30mths, $p=0.001$), EGFR (13 vs 25 mths, $p=0.043$), mesothelin (13 vs 26 mths, $p=0.001$), Ca125 (17 vs 37mths, $p<0.001$), and FOXC1 (7 vs 25mths, $p=0.003$). Two-step cluster analysis revealed four distinct patterns of biomarker expression, each associated with different survival outcomes: (1) S100A4+ Ca125+ Mesothelin+ (mOS 12mths); (2) S100A4+ Ca125+ Mesothelin- (mOS 17mths); (3) S100A4+ Ca125- Mesothelin- (mOS 33mths); (4) S100A4- Ca125- Mesothelin- (mOS 40mths); log-rank $p<0.001$.

Conclusion: S100A4, Ca125 and Mesothelin immunohistochemistry reveals patterns of biomarker expression that predict survival after resection. Those patients expressing all three proteins represent a cohort of patients unlikely to derive significant benefit from pancreatic resection. As these proteins are secreted, these should be further evaluated for their prognostic utility in blood.



23. TARGETING OF THE EPIGENETIC HISTONE 3 LYSINE 9 METHYLTRANSFERASE PATHWAY IN KRAS-INDUCED CELL GROWTH AND PANCREATIC CANCER

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Background: Pancreatic ductal adenocarcinoma (PDAC) ranks fourth as a cause of cancer death in the USA and is almost universally fatal, with the annual number of deaths equivalent to the number of newly diagnosed cases. Valuable research has revealed genetic aberrations that contribute to PDAC development and progression, with KRAS being one of the most frequent mutations in more than 90% of patients. However, to date, any efforts to directly target KRAS have failed in the clinic. Thus, there is an urgent need to further improve our understanding of molecular mechanisms underlying PDAC development as to identify novel therapeutic targets, including druggable important downstream targets orchestrated by oncogenic KRAS. In the current study, we examine the epigenetic dimethyl-H3K9 (H3K9me2) histone methyl transferase (HMT), G9a in the context of Kras-induced signaling, cell growth and PanIN formation.

Methods: Using a cell model that allows inducible expression of mutant KRASG12D, affinity protein purification combined with mass spectrometry was used to analyze changes in the composition of G9a complexes. We developed a pancreas-specific G9a knockout, which was evaluated by immunohistochemistry, RNA-seq, and western blot. MTS assays were utilized to monitor the effects of various G9a inhibitors in the absence and presence of activated Kras. To evaluate consequences on gene expression and regulation, a G9a pharmacological inhibitor, BRD4770, and siRNA-mediated G9a knockdown were combined with qPCR and chromatin immunoprecipitation (ChIP) assays. Subcutaneous xenografts were established and treated with vehicle or a G9a pharmacological inhibitor to evaluate in vivo tumor growth.

Results: Activation of oncogenic Kras results in increased protein levels of G9a and its complex partners, as well as stable complex formation. Pdx1-CRE/LSL-KRASG12D crossed with G9a^{fl/fl} mice demonstrate that loss of the H3K9Me2 mark in exocrine cells is accompanied by significantly reduced number of PanIN lesions. RNA-Seq from these animals reveal reduced levels of typical molecular markers of PanIN and upregulation of p21, a cyclin-dependent kinase inhibitor that facilitates cell cycle arrest. Levels of p21 protein are also increased in lysates from Pdx1-CRE/LSL-KRASG12D/G9a^{-/-} animals compared to control mice. G9a inhibition with BRD4770 and siRNA-mediated knockdown in cells recapitulates this effect with p21 upregulation. Furthermore, we find G9a and its H3K9Me2 mark occupy the p21 promoter, suggesting G9a is involved in direct regulation of this gene. Congruently, BRD4770 displays an inhibitory effect on KRASG12D-induced cell proliferation, organoid viability as well as pancreatic tumor growth in a subcutaneous xenograft model.

Conclusion: Combined, these data provide evidence for a key role of the H3K9me-G9a pathway as a mediator of the oncogenic Kras response and defines a novel point of potential therapeutic intervention for PDAC.

24. CHEMOTHERAPEUTIC TREATMENT OF PANCREATIC CANCER AND ITS MICROENVIRONMENT

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Background: FOLFIRINOX and gemcitabine plus nab-paclitaxel are newer treatments in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). Despite only being effective in 32% and 23% of patients respectively, there is a lack of evidence guiding the use of one drug over the other. The aim of this study is to stratify the sensitivity of PDAC cell lines to these drug regimens and to investigate the role of the tumor microenvironment in their efficacy.

Methods: The growth of low-passage patient-derived cell lines treated with increasing doses of FOLFIRINOX and gemcitabine-paclitaxel (Gem-Pac) for 5 days was evaluated by resazurin assay. The chemosensitivity of a subset of PDAC cell lines was evaluated using conditioned media from cancer associated fibroblast (CAF) and hepatic stellate cell (HSC) cultures.

Results: The maximum growth inhibition achieved (EMax) and the amount of drug needed to achieve 50% cellular growth inhibition (GI50) were determined for 18 cell lines. A high EMax (>75%) and low GI50 (≤ 16 nM FOLFIRINOX, ≤ 1.5 nM Gem-Pac) was used to define optimal sensitivity to these drugs: 2 cell lines were optimally sensitive to both drugs, 7 exhibited optimal sensitivity to FOLFIRINOX but sub-optimal sensitivity to Gem-Pac, and 2 exhibited optimal sensitivity to Gem-Pac but sub-optimal sensitivity to FOLFIRINOX. To investigate the impact of the tumor microenvironment on PDAC chemosensitivity, we examined changes in the efficacy of these drugs in the presence of conditioned media from tumor-derived CAFs and liver-derived HSC. While conditioned media resulted in only modest changes in EMax, they had a significant impact on GI50. Out of 4 PDAC cell lines treated in conditioned media from 2 independent CAF lines, 1 exhibited a more than 2-fold increase in GI50 in response to FOLFIRINOX. Moreover, when treated in HSC conditioned media, 2 cell lines exhibited as much as a 6-fold increase in resistance to FOLFIRINOX and 1 exhibited a 2-fold increase in resistance to Gem-Pac. Based on the observation that resected tumor samples from patients treated with FOLFIRINOX generally exhibit a dearth of activated fibroblasts, we examined the effects of FOLFIRINOX on CAF cultures. The GI50 of CAF cultures were dramatically decreased (50-75%) in response to FOLFIRINOX when grown in conditioned media from 3 out of 6 PDAC cell lines. In contrast, conditioned media from 2 PDAC cell lines increased the GI50 of CAF cultures by as much as 50% in response to FOLFIRINOX.

Conclusion: Subgroups of PDAC cell lines exhibit preferential sensitivity to one combination chemotherapy over another, reflecting the heterogeneity of patient response to these drugs. This heterogeneity is echoed by the variable impact CAF and HSC have on in vitro drug efficiency in select PDAC cell lines, encouraging further investigation of the distinct relationships between cancer cells and their associated microenvironments in the context of chemotherapeutic treatment.

25. IDENTIFYING A SEQUENCE ALTERATION IN THE REGULATORY DOMAIN OF CELL CYCLE INHIBITOR, WEE1, COULD DEFINE A NOVEL FAMILIAL, LYNCH-LIKE SYNDROME AND HAVE IMPLICATIONS FOR THE TREATMENT OF PANCREATIC CANCER

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Background: The RNA-binding protein Human Antigen R (HuR) is upregulated in pancreatic ductal adenocarcinoma (PDA), where it promotes tumorigenesis via its mRNA pro-survival targets. PDA cells exposed to stressors of the tumor microenvironment upregulate the mitotic inhibitor kinase, WEE1, in a HuR-dependent manner to induce cell cycle arrest and facilitate drug-resistance [Lal, et. al Cancer Research. 2014;74(4):1128-1140.]. We have previously identified a 56 base-pair (bp) region within WEE1's 3' untranslated region (labeled WEE1.3UTR) where HuR binds and stabilizes expression. Within this regulatory site, we observed that a 10-thymidine (T) track contains frequent polymorphisms (mean allele frequency 8.67%) of thymidine insertions (i.e, an INDEL).

Methods: Using a combined approach of Sanger-sequencing and a more sensitive capillary-electrophoresis (CE) assay, we evaluate this region in various cancer cell lines and a cohort of resected patient tumor samples (n=99). To compare how these alleles may be differentially regulated in vitro, domains harboring these sequences are isolated and tagged with fluorescent dyes in order to relate measured fluorescence to function. Complementary RNA-binding protein immunoprecipitation (RNP-IP) assays are performed to validate HuR association to the constructs. Moreover, we evaluate how cell lines of different genotypes respond to treatment with various DNA-damage agents in order to correlate sensitivity.

Results: Evaluation of 10-T track in human PDA cell lines reveal three distinct alleles between individual cohorts: the wild-type (10-T, 56 bps), a 1-T insertion (11-T, 57 bps), and a 2-T insertion (12-T, 58 bps). Within the patient cohort, we find a significant enrichment for individuals homozygous for 12-T among those with a unique, Lynch-like familial history of cancer (odds ratio 2.4-6.9, $p < 0.05$). In response to a stressor, constructs with the wild type allele report a higher level of expression compared to the 11-T and 12-T alleles ($p < 0.01$). Lastly, we find a correlation of increased sensitivity to genotoxic treatment in lines with one or two copies of 11T or 12T, as compared to those wild-type for 10T.

Conclusion: We postulate that the addition of the INDEL in the WEE1.3UTR disrupts the association of HuR, and therefore, the functional upregulation of the WEE1 transcript in response to the stressful PDA microenvironment. Thus, a dysregulated G2/M checkpoint could result in accumulated DNA-damage and eventually promote PDA tumorigenesis. Paradoxically, the disruption of the HuR-WEE1 axis may render PDA cells more sensitive to genotoxic agents, thus providing a potential therapeutic window for patients screened for the polymorphism.

26. ADENOSQUAMOUS CARCINOMA OF THE PANCREAS: FIRST SUCCESSFUL PDX MODELS WITH CHARACTERIZATION

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Background: Adenosquamous carcinoma of the pancreas (ASCP) is a rare and lethal histologic subtype of pancreatic cancer. ASCPs are defined by a mix of at least 30% malignant squamous cell carcinoma and coexisting ductal adenocarcinoma. As normal pancreas tissue has no benign squamous epithelial components, the origin of this tumor is uncertain. Postoperative recurrence rates are high and ASCP demonstrates significantly worse overall survival compared to ductal adenocarcinoma. The low prevalence of ASCPs makes research studies and clinical trials exploiting unique features of this tumor difficult. We aimed to generate the first known PDX models of ASCP in order to (1) genomically characterize (2) functionally assess for chemosensitivity and (3) correlate functional assay sensitivity with therapeutic response using tumor bearing ASCP mice.

Methods: Patient derived xenografts (PDX) were generated from surgical resection of patient tumor tissue in NOD/SCID mice. All patient and derived PDX tumors were histologically (H&E and IHC) confirmed. We performed whole genome mate pair sequencing (MPseq) on PDX tissues. Western blot and immunohistochemistry for the presence of MTH1 enzyme was performed to identify possible sensitivity to MTH1 inhibition. Cells were cultured using a hanging drop technique and treated with cytotoxic and targeted therapies. Cell viability was assessed using daily cell counts and Prestoblu dye.

Results: Five ASCP PDX models were created with 100% initial engraftment rate and >90% engraftment ratio. Histomorphology and Immunohistochemistry for p63 (squamous) and mucin components accurately recapitulated the ASCP phenotype from the original patient tumors. MPseq revealed distinct patterns of aneuploidy and all losses in 17p, 18q and 21q. Each predicted homozygous loss of p16 (CDKN2A) (9p21.3) and heterozygous losses of both TP53 and SMAD4. Two models also predicted double and single losses of PTEN. Western blot and immunohistochemistry revealed variable MTH1 expression. Cellular spheroids and 2D cultures demonstrated cytostatic sensitivity to the combination of gemcitabine and oxaliplatin as well as the sensitivity to novel MTH1 inhibitors based on MTH1 expression. These findings were confirmed with in-vivo treatment studies in tumor bearing PDX models of ASCP

Conclusion: ASCP is a rare but more malignant phenotype compared to pancreatic adenocarcinoma. We have generated the world's first successful models of ASCP. Whole genome sequencing reveals common genomic aberrations. Functional assays using three dimensional organoids demonstrate cytotoxic as well as targeted monotherapy responses. This correlated with therapeutic response in tumor bearing PDX models.

27. PHYSICAL ACTIVITY IS ASSOCIATED WITH IMPROVED QUALITY OF LIFE AND FUNCTIONAL FITNESS AMONG PATIENTS RECEIVING PREOPERATIVE THERAPY FOR PANCREATIC CANCER

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Background: Exercise may help optimize performance status and fitness during preoperative treatment for pancreatic cancer. We sought to evaluate associations between physical activity and changes in health-related quality of life (QOL) and functional fitness among patients participating in a multi-modal, home-based exercise program concurrent with preoperative chemo- or radiation therapy for pancreatic cancer.

Methods: Patients (N=50, mean age 66.4±7.9yrs, 48% female) were encouraged to perform ≥60 min/week moderate-intensity aerobic exercise and ≥60 min/week strengthening exercise during treatment. Patients reported aerobic and strengthening exercise in daily exercise logs throughout treatment, and light and moderate-to-vigorous physical activity were measured using Actigraph GT3X+ accelerometers worn during each treatment phase. QOL and physical functioning were assessed using the FACT-Hep and PROMIS Short Form, respectively, and patients performed a 6-minute walk test (6MWT), 5x sit-to-stand test (5xSTS), and grip strength test upon enrollment and following treatment. Multivariable models evaluated associations between self-reported or accelerometer-measured physical activity and changes in QOL and functional fitness.

Results: 6MWT improved from 459.7 ± 86.4m to 488.2 ± 93.1m (p=.001), and 5xSTS improved from 11.4 ± 4.2s to 10.6 ± 3.6s (p<.05). Aerobic exercise was positively associated with improvements in self-reported physical functioning (B=.02, p=.03) and 6MWT (B=.19, p=.05). Light physical activity was positively associated with improvements in QOL (B=.03, p=.02), self-reported physical functioning (B=.01, p=.02), and 6MWT (B=.08, p=.03). Moderate-to-vigorous physical activity was positively associated with improvements in self-reported physical functioning (B=.03, p<.01) and 6MWT (B=.18, p=.03). Strengthening exercise was not significantly associated with changes in any outcomes, and there were no significant associations between self-reported or accelerometer-measured physical activity and changes in 5xSTS or grip strength.

Conclusion: Self-reported and objective physical activity were associated with favorable changes in QOL and functional fitness among patients participating in a home-based exercise program concurrent with preoperative therapy for pancreatic cancer. Preoperative therapy provides a critical window to optimize and prepare patients for possible pancreatic cancer surgery, and our findings support the use of structured exercise programming to improve QOL and physical functioning in this context.

28. LAPAROSCOPIC VERSUS OPEN PANCREATODUODENECTOMY (LEOPARD-2): A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Background: Laparoscopic pancreatoduodenectomy (LPD) is gaining popularity because of potential advantages including, less operative blood loss, less delayed gastric emptying, and shorter hospital stay but concerns exist regarding increased pancreatic fistula rates and, in low-volume centers, increased postoperative mortality. A recent RCT from one high-volume center recently reported shorter length of hospital stay after LPD, compared to OPD, without differences in morbidity and mortality. In the Netherlands, LPD was introduced according to the IDEAL framework for surgical innovation including a training program (LAELAPS-2) with a 3.5% 90-day mortality and 34% pancreatic fistula rate in the first 114 LPDs in 4 centers. According to the IDEAL framework, we hereafter initiated an RCT to assess whether LPD could reduce time to functional recovery.

Methods: A multicenter randomized controlled, patient-blinded, trial comparing LPD with OPD was performed in 4 centers that each perform ≥ 20 pancreatoduodenectomies annually (median 37 (range 23-77)), completed the LPD training program, and had performed at least 20 LPDs during the 18 months training period (range 23-34). Adult patients with an indication for pancreatoduodenectomy because of a neoplasm without signs of vascular involvement were included. Primary outcome was time (days) to functional recovery.

Results: The data safety monitoring board (DSMB) recommended early termination of the trial because of a difference in 90-day complication-related mortality (LPD 5 (10%) vs. OPD 1 (2%), $P=0.2$). The DSMB stated that the possible harm for patients did not outweigh the hypothesized patient benefit. In total, 99 of the projected 136 patients were included (50 LPD and 49 OPD). Time to functional recovery was 9 days (95% CI 6-12) after LPD vs. 8 days (95% CI 6-10) after OPD ($P=0.9$). The conversion rate with LPD was 20%. Operative blood loss was 300 mL (IQR 200-531) vs. 400 mL (300-975) ($P=0.2$) and operative time 391 (IQR 226 - 451) vs. 235 (IQR 205 - 317) minutes ($P=0.001$) for LPD and OPD respectively. Clavien-Dindo grade ≥ 3 complications were seen in 25 (50%) vs. 20 patients (41%) ($P=0.4$), pancreatic fistula grade B/C in 15 (30%) vs. 14 (29%) ($P=0.9$), hepaticojejunostomy leakage grade B/C in 5 (10%) vs. 6 (12%) ($P=0.2$) and postpancreatectomy haemorrhage grade B/C in 6 (12%) vs. 7 (14%) ($P=0.7$), for LPD and OPD respectively. Hospital stay was 11 days (IQR 7-20) after LPD and 10 (IQR 7-17) after OPD ($P=0.6$). The median annual volume of LPD per center during the trial was 11 (range 6-15).

*90-day follow-up incomplete for 6 pts.

Conclusion: This early terminated multicenter RCT showed no difference in time to functional recovery between LPD and OPD, and no statistically significant differences for morbidity and mortality. The mortality rate after LPD raises concerns, especially in the absence of patient benefits, highlighting that implementation of LPD should be performed with caution in selected centers.

29. MINIMALLY INVASIVE VERSUS OPEN DISTAL PANCREATECTOMY (LEOPARD): MULTICENTER PATIENT-BLINDED RANDOMIZED CONTROLLED TRIAL

T de Rooij, J. van Hilst, HC van Santvoort, PB van den Boezem, F Daams, RM van Dam, CH Dejong, EB van Duyn, CH van Eijck, S Festen, MF Gerhards, B Groot Koerkamp, IH de Hingh, G Kazemier, JM Klaase, RH de Kleine, CJ van Laarhoven, MD Luyer, GA Patijn, P Steenvoorde, M Suker, M Abu Hilal, OR Busch, MG Besselink
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Background: Minimally invasive distal pancreatectomy (MIDP) is gaining popularity, but it is unknown whether it is superior to open distal pancreatectomy because randomized studies are lacking.(1) In the Netherlands, MIDP was safely introduced according to the IDEAL framework, within a nationwide training program.(2) Following this standardized introduction, we aimed to compare MIDP and ODP in a randomized setting.

Methods: In this multicenter randomized controlled trial, we assigned adult patients with tumors confined to the left side of the pancreas to MIDP or ODP. Patients were blinded using a large abdominal dressing and treated according to enhanced recovery principles. Primary endpoint was postoperative time to functional recovery (defined as: independently mobile, pain control with oral medication alone, maintaining at least 50% of the daily required intake, no intravenous fluids, and no clinical signs of infection). Follow-up was until 90 days postoperatively. Analyses were according to intention-to-treat.(3)

Results: A total of 108 patients from 14 centers were enrolled, 51 were assigned to MIDP and 57 to ODP. Time to functional recovery was 4 days (IQR 3-6) after MIDP vs. 6 days (IQR 5-8) after ODP ($P<0.001$). MIDP was associated with an improvement of each individual component of the primary endpoint, as well as length of hospital stay (6 days after MIDP vs. 8 days after ODP, $P<0.001$). For MIDP, 10% was robot-assisted and 8% converted to ODP. Operative blood loss was less after MIDP (150 (IQR 50-350) mL for MIDP vs. 400 (IQR 200-775) mL for ODP, $P<0.001$), whereas operative time was longer (217 (IQR 135-277) minutes for MIDP vs. 179 (IQR 129-231) minutes for ODP, $P=0.005$). Grade B/C postoperative pancreatic fistula was seen in 37% of MIDP patients vs. 21% of ODP patients ($P=0.06$), without difference in radiological drainage (22% vs. 20%, $P=0.73$) and re-operation (2% vs. 5%, $P=0.62$). Grade B/C delayed gastric emptying was seen less frequently after MIDP (4% for MIDP vs. 20% for ODP ($P=0.01$)). Clavien-Dindo grade ≥ 3 complications were seen in 25% vs. 38% ($P=0.21$) and mortality in 0% vs. 2% ($P>0.99$), for MIDP and ODP respectively.

Conclusion: MIDP was superior to ODP, indicating that minimally invasive distal pancreatectomy is the preferred treatment for patients with tumors confined to the left side of the pancreas.

This investigator-initiated study registered in the Netherlands Trial Registry (NTR5188).

References

- (1) RÅ_sok B et al. *HPB (Oxford)*. 2017;19(3):205-14.
- (2) De Rooij T et al. *Ann Surg*. 2016;264(5):754-62.
- (3) De Rooij T et al. *Trials*. 2017;18(1):166.

30. MINIMALLY-INVASIVE VERSUS OPEN PANCREATODUODENECTOMY: A PAN-EUROPEAN PROPENSITY-SCORE MATCHED ANALYSIS IN HIGH-VOLUME CENTERS

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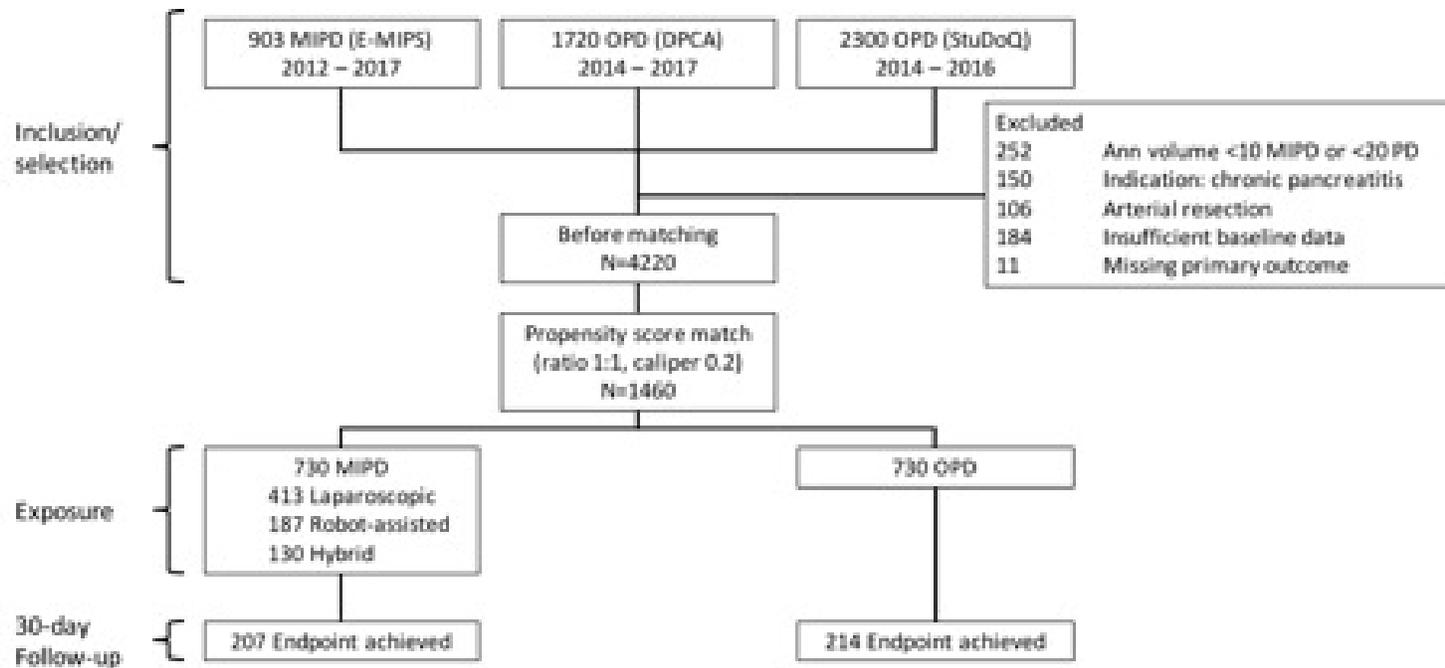
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Background: Multicenter matched studies comparing outcomes of minimally invasive (laparoscopic, robot-assisted, hybrid) pancreatoduodenectomy (MIPD) and open pancreatoduodenectomy (OPD) are scarce. We assessed short-term outcomes among European high-volume (>10 MIPDs and >20 PDs overall per year) centers.

Methods: Multicenter propensity-score matched (1:1) retrospective study on MIPD vs OPD for (pre-)malignant tumors or cysts. We collected MIPD data from 14 European high-volume centers (2012-2017) and OPD data from Dutch and German nationwide pancreatic surgery registries (2014-2017). Propensity scores were based on age, sex, BMI, ASA, comorbidities, ECOG, tumor location, suspected cancer, organ involvement, and venous resection. Primary outcome was 30-day major morbidity (Clavien-Dindo 3a-5). Secondary outcomes included grade B/C pancreatic fistula (POPF), R1-resection (<1 mm) margin, hospital stay and 30-day mortality.

Results: Of 4220 included patients, all 730 MIPD (413 laparoscopic, 184 robot-assisted, 130 hybrid) were matched to 730 OPD. Major morbidity (28% vs 29%, $P>0.729$), mortality (4.0% vs 2.9%, $P=0.314$), R1-resections (20 vs 23%, $P=0.269$), and hospital stay (mean 17 vs 17 days, $P>0.99$) were similar. The rate of POPF was higher after MIPD (23% vs 14%, $P<0.001$). The association between MIPD and major morbidity (OR 0.95, $P=0.686$), mortality (OR 1.57, $P=0.121$), and POPF (OR 1.84, $P<0.001$) remained similar after excluding, respectively, lower volume (10-20 MIPD/year) centers, first 10 MIPD cases, hybrid cases, hybrid and laparoscopic cases. The rates of major morbidity (27% vs 27% vs 35%), POPF (23% vs 19% vs 25%) and 30-day mortality (3.6% vs 5.4% vs 5.6%) were similar between laparoscopic, robot-assisted and hybrid procedures.

Conclusion: In this largest propensity-matched study on MIPD vs OPD to date, we found no significant differences in major morbidity, mortality, R1-resection rate, and hospital stay, but a higher rate of POPF after MIPD. No differences were found between robot-assisted, laparoscopic and hybrid MIPD. MIPD can safely be performed in high-volume centers, but the increased rate of POPF should be addressed.



31. DECODING GRADE B PANCREATIC FISTULA: A CLINICAL AND ECONOMICAL ANALYSIS AND SUB-CLASSIFICATION PROPOSAL

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Background: The 2016 ISGPS refined definition of grade B fistula (B-POPF) is predicated on various post-operative management approaches, ranging from prolonged drainage to interventional procedures. However, the spectrum of clinical severity within this entity is yet undefined. Aim of this study was to describe characteristics and management approaches for B-POPF and investigate whether it segregates into distinct subclasses.

Methods: All consecutive pancreatectomies performed at two institutions from 2007-2016 were reviewed to identify B-POPFs and their treatment strategies. Sub-classification of B-POPFs into three subclasses was modeled after the Fistula Accordion Severity Grading System (B1: prolonged drainage only; B2: antibiotics/artificial nutrition/somatostatin analogues/transfusions; B3: percutaneous/endoscopic/angiographic procedure). Clinical and economic outcomes, unique from the ISGPS definition qualifiers, were analyzed across the subclasses.

Results: B-POPF developed in 320/1949 patients (16.4%), and commonly required prolonged drainage (67.8%), antibiotics (70.3%) and artificial nutrition (54.7%). Percutaneous drainage occurred in 79 patients (24.7%) - always in combination with other strategies. Management of B-POPFs was widely heterogeneous with a median of 2 approaches/patient (range 1-6) and 38 various strategy combinations used. Subclasses B1-3 comprised 19.1%, 52.2% and 28.8% of B-POPFs, respectively, and were associated with progressively worse clinical and economic outcomes (Table). These results held true when analyzing pancreatoduodenectomies and distal pancreatectomies separately, and were confirmed by multivariable analysis adjusted for clinical and operative factors. Notably, distribution of the B-POPF subclasses was influenced by institution and type of resection ($p < 0.001$), while clinical/demographic predictors proved elusive.

Conclusion: B-POPF is a heterogeneous entity, where three distinct subclasses with increasing clinical and economic burden can be identified. This classification framework has potential implications for accurate reporting, comparative research and performance evaluation.

Table. Clinical and economic outcome measures stratified by subtype of grade B fistula

Outcome measure n (%)	Total Grade B 320 (100)	B1 61 (19.1)	B2 167 (52.2)	B3 92 (28.8)	p-value
Total strategies used to treat the fistula; median (IQR)	2 (1-3)	1	2 (2-3)	3 (3-4)	<0.001
Occurrence of non-fistulous complications	244 (76.3)	29 (47.5)	135 (80.8)	80 (87.0)	<0.001
Number of non-fistulous complications; median (IQR)	1 (0-2)	0 (0-1)	1 (0-2)	1 (1-3)	0.008
Total drain duration, days median (IQR)	29 (22-39)	26 (23-31)	26 (19-36)	36 (28-58)	0.733
ICU transfer	38 (11.9)	6 (9.8)	14 (8.4)	18 (19.6)	0.025
Duration of index stay, days Median (IQR)	18 (10-28)	9 (7-13)	21 (15-30)	20 (9-33)	<0.001
Readmission	84 (26.3)	12 (19.7)	31 (18.6)	41 (44.6)	<0.001
Multiple readmissions	15 (4.7)	4 (6.6)	1 (0.6)	10 (10.9)	0.001
Fistula-related readmission	67 (20.9)	0	28 (16.8)	39 (42.4)	<0.001
Duration of total stay, days median (IQR)	21 (14-31)	11 (8-14)	24 (16-32)	25 (19-38)	<0.001
PMI, mean \pm SD	0.325 \pm 0.157	0.221 \pm 0.163	0.313 \pm 0.139	0.417 \pm 0.130	<0.001
Fistula ACB mean, \pm SD	0.274 \pm 0.081	0.110 \pm 0	0.260 \pm 0	0.370 \pm 0	<0.001
Fistula as the highest graded complication	254 (79.4)	34 (55.7)	141 (84.4)	79 (85.9)	<0.001
Costs* median (IQR)	2.3452 (1.637-3.318)	1.363 (1.040-1.946)	2.460 (1.801-3.268)	2.892 (2.177-4.294)	<0.001
Cost variation**	+135%	+36%	+146%	+189%	-

PMI, post-operative morbidity index; ACB, average complication burden.

*Costs data are inflation-adjusted and expressed as a proportion to the cost of a non-complicated resection.

**As compared to the patients experiencing no complications.

32. ADDITIONAL VALUE OF 3D-VISION DURING LAPAROSCOPIC PANCREATODUODENECTOMY BIO TISSUE DRILLS (LAELAPS 3D2D): A RANDOMIZED CONTROLLED CROSS-OVER TRIAL

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Background: Laparoscopic pancreatoduodenectomy (LPD) is a technically challenging procedure with concerns about reported higher rates of postoperative pancreatic fistula. The use of three-dimensional (3D) vision may especially improve surgical performance during construction of the pancreaticojejunostomy (PJ) and hepaticojejunostomy (HJ). Yet, data on added value of 3D vision, both for experienced and less experienced laparoscopic surgeons, are lacking.

Methods: We performed an experimental randomized controlled cross-over trial including 20 expert laparoscopic surgeons and 20 surgical residents capable of laparoscopic suturing. All participants received a detailed video instruction, and subsequently performed a PJ and a HJ twice, using 3D- and 2D laparoscopy on artificial organ models (LifeLike BioTissue®) according to the Pittsburgh method. Participants were randomized for the sequence of laparoscopy, i.e., 3D or 2D first. Primary endpoint was the time needed to complete both the PJ and HJ. Procedures were recorded and subsequently anonymized. Performance of participants was assessed using a modified Birkmeyer surgical performance scoring platform by raters, proficient on the procedure, who were blinded for 3D/2D laparoscopy. Participants completed a questionnaire on side effects of 3D laparoscopy.

Results: A total of 60 HJs and 58 PJs were completed. The use of 3D laparoscopy reduced the time to complete the PJ and HJ with 18.5%, from 84.0 to 68.3 minutes (median 12.2 minutes, CI -5.4- -24.2 min, $P = 0.004$ non-parametric Wilcoxon signed-rank test). Performance scoring also increased with 3D laparoscopy (mean 0.78 increase in 5 point Likert scale summary score, $P = 0.001$). This effect was also seen in the subgroup of experts (13.4% reduction, 9.5 minutes, $P = 0.016$), including a 0.91 increase in summary score ($P = 0.015$). Of all participants, 97% stated to prefer 3D laparoscopy whereas 27.3% reported minor side effects, and 6.1% severe side effects (e.g. eye strain).

Conclusion: 3D laparoscopy, as compared to 2D, demonstrated substantial reduction in procedure time of completing both PJ and HJ in bio-tissue, and improved results in surgical performance grades for both experts and trained residents.

33. LAPAROSCOPIC VERSUS OPEN PANCREATODUODENECTOMY: THE PADULAP RANDOMIZED CONTROLLED TRIAL

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Background: Open pancreatoduodenectomy (OPD) is a well established procedure charged with a high rate of severe morbidity and prolonged hospital stay. Laparoscopic pancreatoduodenectomy (LPD) is an emergent and evolving procedure, whose feasibility has been proved. One recently reported RCT comparing LPD vs OPD offered a shorter hospital stay for LPD with no differences in morbidity.

Methods: This study was conducted from February 2013 to September 2017 as a university single-centre, non-stratified, open-label, parallel-group, intention to treat RCT. To avoid bias from learning curve in LPD, all LPD procedures were done by a single-expert surgeon in both laparoscopic and pancreatic surgery, who also participated in OPD, while other expert surgeons in open pancreatic surgery participated in the OPD. Primary end-point of the study was the length of hospital stay (LOS). Secondary end-points were operative time, blood transfusion and postoperative results and quality of pathological resection. A table of randomization was electronically done and patients were assigned to each group immediately after being selected for PD for any indication. Criteria for exclusion to participate were: locally advanced disease on imaging requiring major vascular resection; severe associated chronic disease; other concomitant neoplasia; clear hostile abdomen for laparoscopic approach; and declining to participate. Sample size calculation of 66 patients was based on the primary end-point. PADULAP trial (ISRCTN93168938).

Results: Of 86 patients assessed for PD, 66 were met eligibility criteria and were randomized, 34 to LPD and 32 to OPD. In LPD group, 8 patients were converted to open, but included in the LPD for final analysis. Postoperative results were evaluated at 90-days. The median duration of LOS was longer for OPD than for LPD (17 vs 13.5 days; $p=0.012$). Operation time was longer for LPD than for OPD (486 vs 365 minutes; $p=0.000$). No differences were found in blood transfusion and postoperative specific complications. OPD had worse poor quality outcomes than LPD (14 and 10 patients, respectively; $p=0.04$). Severe Clavien-Dindo III-V complications were higher in the OPD than in the LPD (11 vs 5 patients, respectively; $p=0.04$). Comprehensive Complication Index was higher in OPD than LPD group (29.6 vs 20.6; $p=0.038$). No differences in number of lymph nodes retrieved and R0 rate were found. There were two deaths in the OPD group and none in the LPD group.

Conclusion: LPD is a tremendous technically demanding procedure that is charged with a prolonged operative time and a considerable conversion rate up to 25% when a minimally selection of the patient is done. However, it can be done with no additional risk for the patients and, even, better postoperative outcomes. In this RCT, LPD presented a shorter hospital stay and less severe postoperative complications than OPD. Some of these data support previous results of the first recently reported single-centre RCT.

34. TARGETED TUMOR STROMA DEPLETION IN COMBINATION WITH A WHOLE CELL TUMOR VACCINE ENHANCES EFFECTOR T CELL INFILTRATION IN A MOUSE MODEL OF PANCREATIC CANCER

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Background: The tumor microenvironment (TME) of pancreatic ductal adenocarcinoma (PDAC) is characterized by a desmoplastic reaction that excludes effector immune cell infiltration, thus preventing optimal efficacy of immunotherapy. A human recombinant hyaluronidase (PEGPH20) has been clinically formulated to enzymatically deplete hyaluronan (HA) in the tumor extracellular matrix. We tested the hypothesis that combining the stromal targeting agent PEGPH20 with a GM-CSF secreting allogenic pancreatic tumor vaccine (GVAX) would increase immune cell infiltration and improve survival of PDAC bearing mice.

Methods: C57BL/6 mice were orthotopically transplanted with 2×10^6 murine KPC pancreatic tumor cells to form liver metastases by a hemisplenectomy technique on day 0. Following tumor transplantation, mice were treated subcutaneously with GVAX in combination with intravenous PEGPH20 or the appropriate control. PEGPH20 was given on day 6 and GVAX on post-operative day 7. An immune modulating dose of Cyclophosphamide (Cy) was given the day before GVAX in all groups. Tumor immune lymphocyte infiltration was assessed by immunohistochemistry and flow cytometry. RT-PCR was performed on tumor associated macrophages isolated with CD11b beads. Mice were sacrificed on day 16 for immune and gene expression analysis. Additional survival analysis followed mice until death. PDAC tissue from resected human patients treated with GVAX were stained for HA via immunohistochemistry (IHC). Additionally, whole exome RNA-sequencing was performed on these tissue samples to assess the CXCR4 pathway and correlation with HA expression status.

Results: Combination therapy with PEGPH20 and GVAX yielded higher infiltration of effector CD8⁺ and CD4⁺ tumor infiltrating lymphocytes in the TME compared to untreated and monotherapy groups (all $p < 0.05$). Murine survival was improved in the combination therapy group as compared to GVAX therapy alone (Hazard Ratio: 0.286 [0.10-0.82] $p = 0.02$). Lower CXCR4 expression was noted in myeloid cells of the combination therapy group. Furthermore, in human PDAC tissue, high HA expression on IHC was associated with increased RNA expression of CXCR4.

Conclusion: Our preclinical murine model of PDAC demonstrates enhanced efficacy of GVAX in combination with the stromal targeting agent PEGPH20 with increased immune cell infiltration and a survival advantage. Decreased CXCR4 expression suggests a chemotactic mechanism to CD8⁺ infiltration beyond decreased vascular impedance. The relationship of HA and CXCR4 in human PDAC tissue further supports this possible signaling relationship. This study provides rationale for further study of this combination for PDAC treatment.

Figure 1. Combination therapy of PEGPH20 with Cy/GVAX improves immune cell infiltration and survival in a PDAC mouse model.

Total number of live (A) CD8+ and (B) CD4+ tumor infiltrating lymphocytes after KPC hemispleen surgery and indicated therapy. Data represent mean \pm SEM from one representative experiment with three mice per group that was repeated twice. (C) Kaplan-Meier survival curves of mice that were implanted with PDAC cells and treated with Cy/GVAX with and without combination of PEGPH20. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; ns = not significant

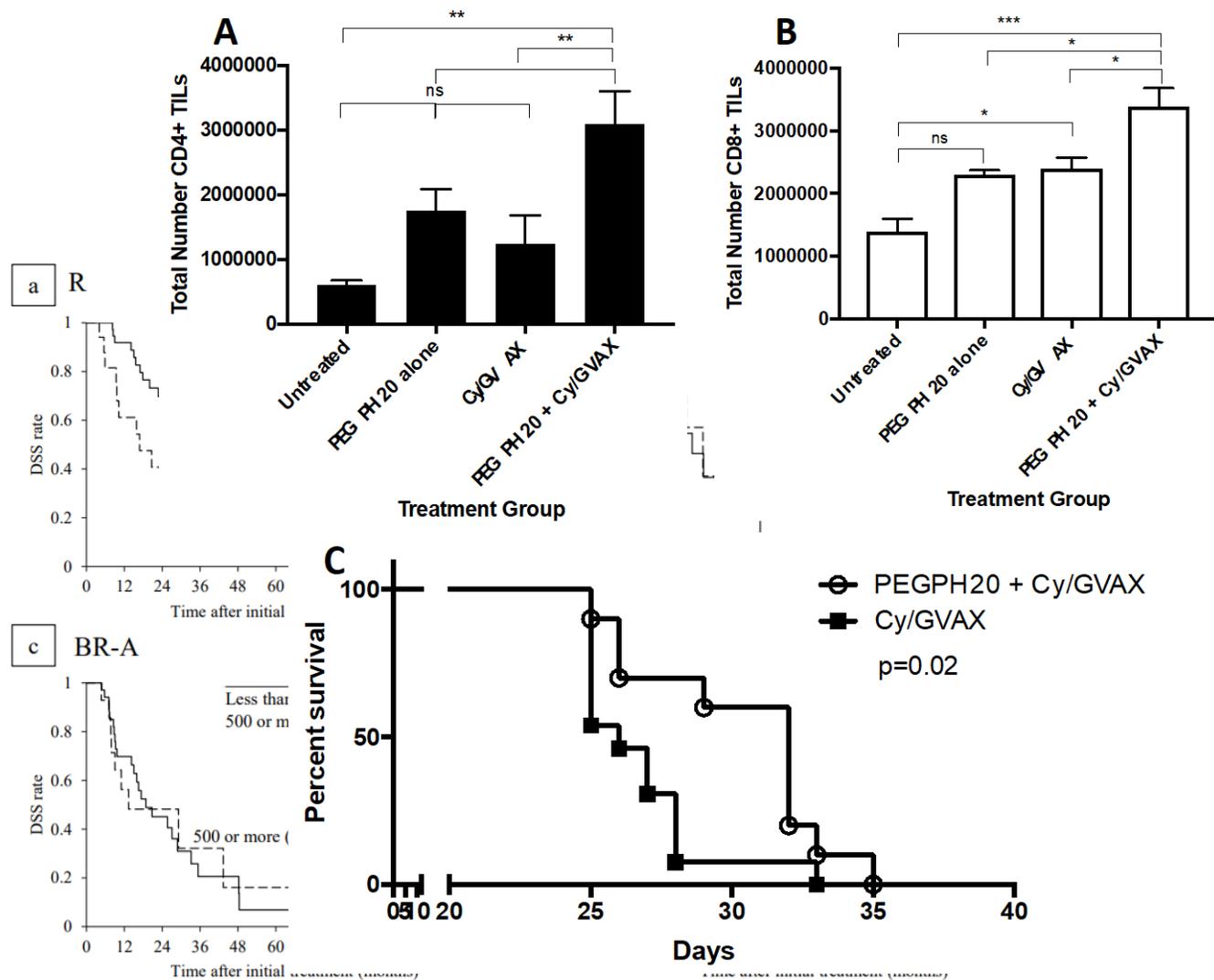


Figure. Disease-specific survival (DSS) curves according to serum CA19-9 level in (a) R (n=57), (b) BR-PV (n=26), (c) BR-A (n=49), and (d) LA (n=139) in the re-evaluated patients excluding the 13 patients whose CA19-9 level was 1 or less U/ml (n=272) (cut-off value of CA19-9 is 500 U/ml)

R: resectable, BR-PV: borderline resectable (superior mesenteric vein/portal vein invasion alone), BR-A: borderline resectable (arterial invasion), LA: locally advanced, MST: median survival time (months), NA: not applicable

35. ERADICATION OF THE GUT MICROBIOME ATTENUATES PANCREATIC CANCER BURDEN THROUGH AN IMMUNE-MEDIATED MECHANISM

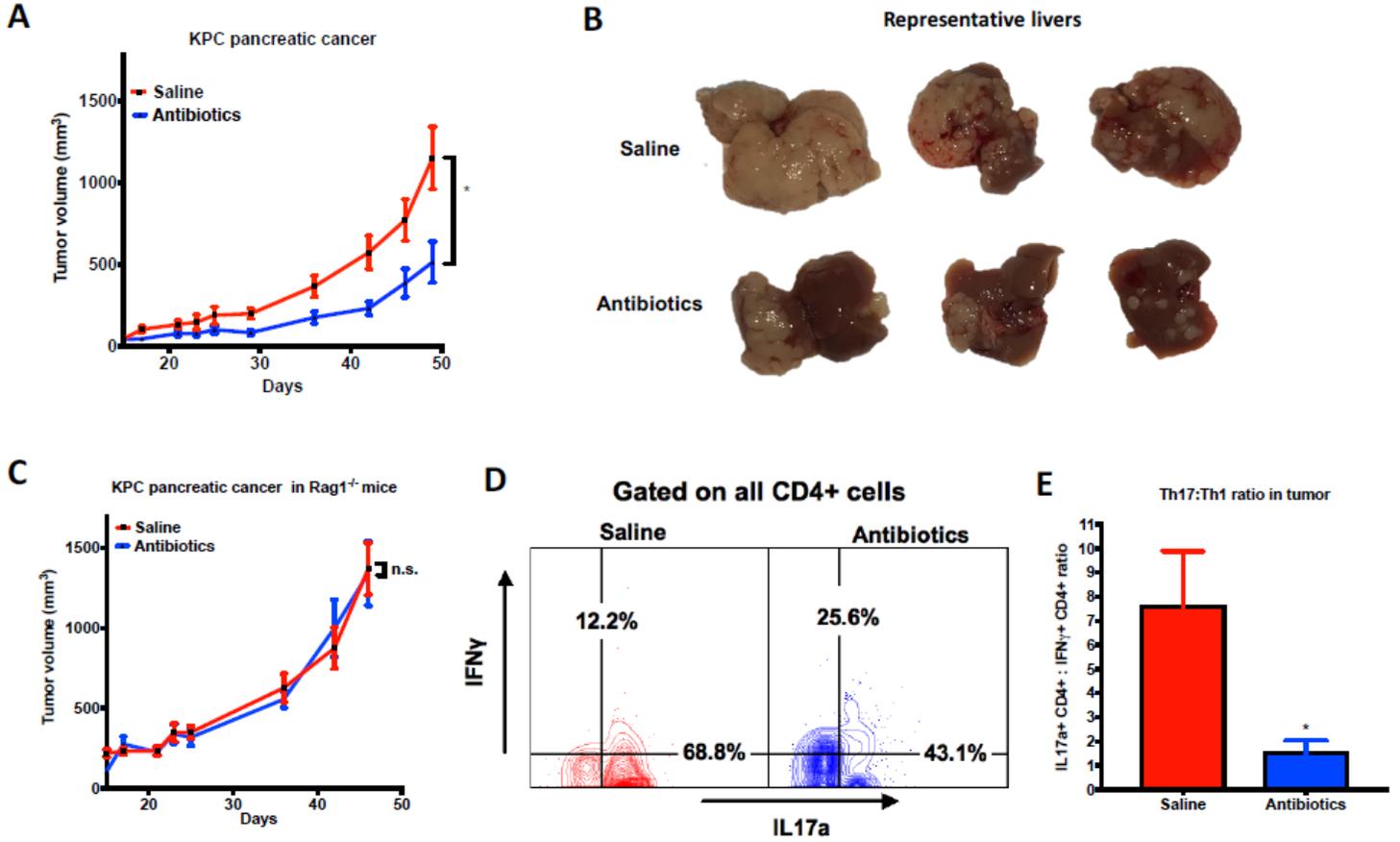
V Sethi, S Kurtom, M Tarique, B Giri, B Garg, S Lavania, A Ferrantella, Z Malchiodi, L Hellmund, HC Jacob, R Dawra, S Banerjee, S Roy, S Ramakrishnan, A Saluja, V Dudeja
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Background: Microbes residing in the gut outnumber ‘human’ cells in our body. This resident microbiota forms a fluctuating metagenome in our gut, amenable to changes in nutrition, age and even geography. Further, many disease states are characterized by a shift in the gut microbiome from a ‘eubiotic’ to ‘dysbiotic’ state. An expanding body of evidence has associated this dysbiosis to the etiopathology of diseases like diabetes, colitis etc. The relationship between pancreatic cancer and the gut microbiome is, however, ambiguous. We aimed to investigate this association.

Methods: Gut microbiota of age and sex matched C57BL/6J mice was depleted by a cocktail of oral, poorly-absorbable antibiotics. KPC pancreatic cancer cells derived from Kras LSL.G12D/+; p53 R172H/+; Pdx::Cre mice were injected subcutaneously as well as intrasplenically for liver metastases into the antibiotic or control mice. These mice were also used to model melanoma and colon cancer. Tumors were immunophenotyped through flowcytometry. To confirm the role of immunity, subcutaneous experiments were simultaneously repeated in C57BL/6J mice carrying a Rag1^{tm1Mom} mutation (Rag1 knockout mice).

Results: Gut microbial ablation decreased tumor burden across multiple cancer models. This effect disappeared when experiments were repeated in Rag1 knockout mice implicating (i) that the tumor-inhibiting effect was not due to an off-target cytotoxic action of antibiotics and (ii) that the phenomenon required a functional arm of the adaptive immune system. Flowcytometry of KPC tumors from wildtype mice revealed a decrease in IL-17 secreting cells, drastic attenuation of Th17:Th1, Tc17:Tc1, IL-10⁺ CD4⁺: IFN γ ⁺ CD4⁺ ratios and decreased M2-macrophages in tumor milieu with gut microbial ablation. A similar decrease in Th17 cells was found in the caeca of antibiotic-given mice. IL-17 is a signature Th17 cytokine produced in response to bacterial and fungal pathogens and has been found to be pro-neoplastic in pancreatic cancer, melanoma and liver metastases whereas Th1 cells orchestrate an anti-neoplastic cytotoxic program in tumor microenvironment in multiple cancers.

Conclusion: Gut microbial modulation promises to form the basis of an important immunotherapeutic strategy against pancreatic cancer and needs to be investigated further.



Gut microbial depletion decreases tumor burden through an immune-mediated mechanism. (A); (B) saline and antibiotics gavaged C57BL/6J mice were (A) subcutaneously implanted with KPC pancreatic cancer cells (n=8-10 per group) or (B) given intrasplenic injection of KPC cells (n=7-9 per group) to induce liver metastases (C) subcutaneous KPC experiment was repeated in saline and antibiotic gavaged Rag1 knockout C57BL/6J mice (n=9-10 per group). (D); (E) Flowcytometry results of KPC tumors from *wildtype* saline or antibiotic-gavaged mice (n=9 for saline group and n=6 for antibiotics group). (Data is shown as mean \pm SEM; *, p<0.05)

36. THE SYSTEMIC IMMUNE-INFLAMMATION INDEX INDEPENDENTLY PREDICTS SURVIVAL AND RECURRENCE IN RESECTABLE PANCREATIC CANCER AND ITS PROGNOSTIC VALUE DEPENDS ON BILIRUBIN LEVELS

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Background: Pancreatic cancer is associated with a dysfunctional immune system and poor prognosis. Our aim was to determine the prognostic significance of several inflammatory biomarkers (i.e. neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Glasgow prognostic score (GPS) and the systemic-immune-inflammation index(SII)) in patients with resectable pancreatic ductal adenocarcinoma (PDAC), using cancer-specific survival as the primary outcome, and the effects of bilirubin on these indices.

Methods: We retrospectively assessed all pancreatic resections performed between 2004-2015 at four tertiary referral centers to identify pathologically confirmed PDAC patients. Baseline clinicopathologic characteristics, pre-operative laboratory values such as absolute neutrophil, lymphocyte and platelet counts, C-reactive protein, albumin, bilirubin and CA19-9 levels, as well as follow up information, were collected. The associations of the calculated inflammatory indices with outcome were both internally and externally validated.

Results: A total of 590 patients with resectable PDAC were included. The discovery and validation cohort included 170 and 420 patients, respectively. Among the inflammatory biomarkers, SII was found to have the strongest prognostic value. $SII > 900$ (Figure 1) (HR 2.32, 95% CI: 1.55 - 3.48), lymph node ratio (HR 3.75, 95% CI: 2.08 - 6.76) and $CA19.9 > 200$ kU/l (HR 1.62, 95% CI: 1.07 - 2.46) were identified as independent predictors of cancer-specific survival. Separate model analysis confirmed that preoperative SII contributed significantly to prognostication. However, SII appeared to lose its prognostic significance in patients with bilirubin levels above $200 \frac{1}{4}$ mol/L.

Conclusion: SII is an independent predictor of cancer-specific survival and recurrence in patients with resectable PDAC. SII may lose its prognostic significance in patients with high bilirubin levels. Properly designed prospective studies are needed to further confirm this finding.

37. THE SYSTEMIC IMMUNE-INFLAMMATION INDEX AS A MARKER FOR EARLY DETECTION OF PANCREATIC CANCER

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Background: Multiple theories have been proposed regarding the association between inflammation and cancer. One hypothesis is that low-grade, chronic inflammation increases the risk of cancer. An alternative hypothesis is that the inflammation is a consequence, rather than the cause, of cancer. Irrespective of whether inflammation causes cancer, studies found that inflammatory markers in blood can be used as biomarkers for early cancer detection.

A relatively novel inflammatory marker in this field is the systemic immune-inflammation index (SII). It is an index that incorporates the absolute blood counts of neutrophils (N), lymphocytes (L) as well as platelets (P). The SII is a prognostic factor after surgery in patients with hepatocellular carcinoma, colorectal, and pancreatic cancer. It has recently been shown that healthy individuals with a high value of the SII have an increased risk of being diagnosed with a solid cancer, especially in the first 6 months after blood draw. Therefore we aimed to assess whether the SII can be used as a marker for early detection of pancreatic cancer.

Methods: Data were obtained from the Rotterdam Study; a population-based prospective cohort study of individuals aged 45 years and above. Absolute blood counts were used to calculate the SII at baseline using the following formula: $P * N/L$. We used the prospectively collected blood count measurements from the Rotterdam Study and complemented those with measurements that were collected retrospectively from the patient files. We used a mixed linear model to assess whether the SII measurements increased over time up till the diagnosis of pancreatic cancer.

Results: At baseline 14,924 participants were at risk of developing pancreatic cancer, of whom 6101 were male (40.9%) and 8821 were female (59.1%). The mean age was 66.0 years (SD 10.5) and the median follow-up time was 16.4 person years (SE 0.2) per person. In total 113 participants developed pancreatic cancer: 38.9% male and 61.1% female. The mean age at diagnosis was 77.3 years (SD 8.8). Almost all patients had metastasized disease, only 8 patients had a complete resection (7.1%). The median survival was 71 days (SE 11.6). The reference values of the SII in the general population were 189 - 1168. At diagnosis of pancreatic cancer SII levels were much higher; with a median of 1466 (IQR: 1150 - 2448). For 44 participants we had one or more SII measurements in the two years prior to diagnosis. There was a significant increase of the SII during that time (P-value = 0.0183). This association remained significant after adjustment for age and sex (P-value = 0.0097).

Conclusion: These preliminary results show that the SII might be a useful marker in the early detection of pancreatic cancer.

38. IMPROVED THERAPEUTIC EFFICACY OF T-CELLS DERIVED FROM HUMAN PANCREATIC CANCER DRAINING LYMPH NODES IN COMBINATION WITH IMMUNE MODULATORS IN A XENOGRAFT MODEL OF METASTATIC HUMAN PANCREATIC CANCER

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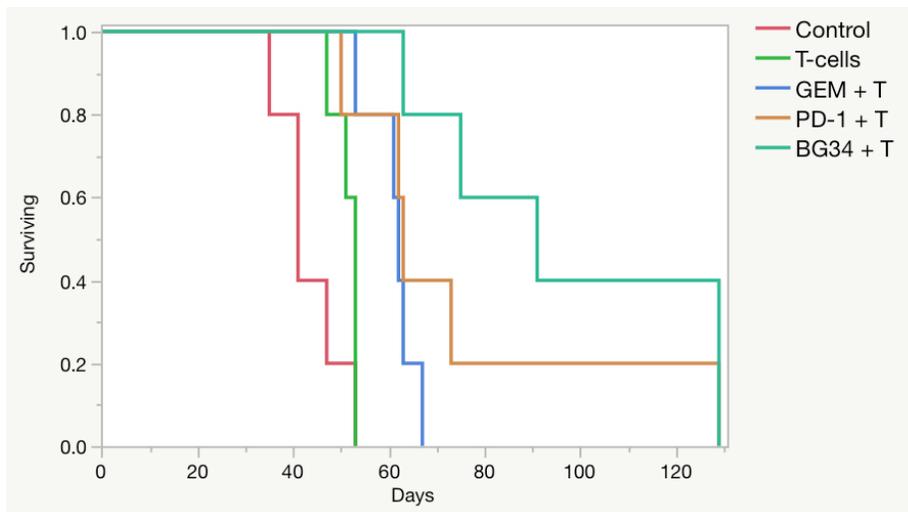
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Background: Adoptive t-cell transfer has demonstrated responses in patients with melanoma, however its efficacy in treating pancreatic cancer (PC), a less immunogenic tumor, is unclear. The purposes of this study are to test the efficacy of t-cells derived from human pancreatic cancer draining lymph nodes (PDLN) in a mouse xenograft model of metastatic human PC and to determine if efficacy is enhanced in combination with immune modulators.

Methods: PDLN were obtained from patients undergoing pancreaticoduodenectomy for PC. SCID mice bearing a human PC cell line (AsPc1) were treated with ex vivo expanded PDLN-derived human t-cells. Mice were also treated with anti-PD1 antibody, Gemcitabine, or an immune modulator BG34 (beta glucan), alone or in combination with subtherapeutic doses of t-cells. The primary endpoint was overall survival.

Results: Mice treated with t-cells exhibited a dose-dependent increase in survival compared to controls ($p=.001$). Anti-PD1 antibody in combination with a subtherapeutic dose of t-cells significantly improved survival compared to t-cells alone ($p=.04$) and untreated control ($p=.01$), although anti-PD1 alone did not ($p=.86$). BG34 alone did not significantly increase survival compared to control ($p=.16$), however combination therapy with BG34 and t-cells markedly increased survival ($p=.002$). Gemcitabine alone improved survival compared to control ($p=.01$) but this effect was not enhanced when combined with t-cells ($p=.53$). Flow cytometry revealed human t-cells persisting in tumor tissue, with a predominantly CD8+ phenotype. Immunohistochemistry confirmed the presence of tumor-infiltrating adoptively transferred human lymphocytes.

Conclusion: T-cells derived from human PDLNs increase the survival of mice bearing human PC xenografts in a dose-dependent manner. The therapeutic efficacy of transferred PDLN cells is significantly enhanced when combined with certain classes of immune modulators. These findings support the investigation of immune modulators in adoptive immunotherapy treatment strategies in patients with pancreatic cancer.



39. INHIBITION OF SDF-1/CXCL12 ENHANCES IMMUNE RESPONSE IN PANCREATIC DUCTAL ADENOCARCINOMA

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Background: Pancreatic ductal adenocarcinoma (PDAC) is believed to be an immunologically "cold" tumor. This, in part, is mediated by the dense, fibrotic stroma that helps maintain an immune-suppressed microenvironment. SDF-1/CXCL12 has been shown to act as a chemo-repellent in several cancers. Therefore, we evaluated the role of stromal SDF-1/CXCL12 in mediating an immunosuppressive phenotype within the pancreatic tumor.

Methods: Pancreatic cancer cells harvested from KPC, a genetically engineered mouse model for PDAC, were either injected alone or co-injected with pancreatic stellate cells (PSCs) extracted from WT (C57/BL6) mice to induce tumors. IF and q-RT PCR were used to evaluate SDF-1 expression in the tumor. An SDF-1 inhibitor, AMD3100 (2mg/kg), or vehicle was administered i.p. for 21 days in tumor-bearing mice. At the end point, tumor growth was measured, and immune infiltration was assessed by flow cytometry. To evaluate T cell migration in vitro, PSCs were pre-treated with SDF-1 neutralizing antibody, educated with KPC cancer cells, and further co-cultured with splenic CD3+ T cells extracted from KPC mice in a transwell system.

Results: In vitro results showed markedly increased secretion of SDF-1 by PSCs, and neutralization of SDF-1 led to increased T-cell migration when cultured with cancer cells alone. In vivo, we also evaluated the effect of inhibition of the SDF-CXCR4 axis on tumor growth. Co-injection of KPC with WT PSC formed larger tumors with increased secretion of SDF-1 as compared to when KPC cells were injected alone. Interestingly, inhibition of SDF-1-CXCR4 interaction with AMD3100 led to reduced tumor growth with increased infiltration of activated CD8+ cytotoxic T cells as compared to the saline-treated mice.

Conclusion: Our findings indicate that stromal cells contribute to tumor progression by blocking the infiltration of cytotoxic T cells via secretion of SDF-1/CXCL12. Targeting SDF-1/CXCL12 could pave the way for designing better therapeutic strategies against pancreatic ductal adenocarcinoma.

40. IMMUNOLABELING OF CLEARED HUMAN PANCREATA PROVIDES INSIGHTS INTO THREE-DIMENSIONAL PANCREATIC ANATOMY AND PATHOLOGY

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Background: Since the days of Rudolph Virchow, pathologists have studied diseases in two dimensions (2D). Visualizing pathologies in three dimensions (3D), however, can provide unique insights into the biology of human diseases. We cleared and immunolabeled thick (~0.5cm) sections of surgically resected human pancreata and visualized normal pancreas, pancreatic intraductal neoplasms and invasive carcinomas in 3D.

Methods: A rapid and easy to implement dibenzyl ether (DBE) based technique was used to clear thick sections of surgically resected human pancreatic parenchyma. Protocols were optimized for both fresh and formalin-fixed, paraffin-embedded (FFPE) tissue. The penetration of antibodies for immunolabeling, such as antibodies to CK19, through the dense desmoplastic stroma was optimized by applying centrifugal and convection flow. Immunolabeling was visualized in 3D using the LaVision Ultramicroscope II (Light Sheet Microscopy) and the Zeiss LSM800 (Laser Scanning Microscope). 3D reconstruction and animations were prepared with Bitplane Imaris software.

Results: The technique was successfully applied to 26 sections of pancreas, providing visually stunning 3D images of normal pancreatic tissue, pancreatic intraepithelial neoplasia (PanIN; <https://youtu.be/o4hJrit2x7o>), intraductal papillary mucinous neoplasms (IPMNs) and infiltrating pancreatic ductal adenocarcinomas (PDACs) (<https://youtu.be/yDB2au3aPgw>). The visualization of disease in 3D highlighted processes, such as invasive carcinoma growing into pre-existing pancreatic ducts (<https://youtu.be/06Ml6lCxBOE>) and in blood vessels (<https://youtu.be/aGHLkeldyYs>), which are hard to conceptualize in 2D.

Conclusion: Three dimensional visualization of cleared human solid organs provides an extraordinary opportunity to understand the true complexity of human disease. Expanding this technique to FFPE tissue opens pathology archives to 3D visualization of unique biosamples and rare diseases. The application of immunolabeling and clearing to human pancreatic parenchyma, as we present here, provides detailed visualization of normal pancreatic anatomy, and can be used to characterize the three dimensional architecture of disease processes ranging from PanIN and IPMN to PDAC.

41. DOES INTRAOPERATIVE SURGICAL DISSEMINATION IN PANCREATIC DUCTAL ADENOCARCINOMA COMMONLY OCCUR?

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Background: The exceptionally high recurrence rate after resection of pancreatic ductal adenocarcinoma (PDA) has been attributed to aggressive intrinsic biology. However, surgical dissemination remains an unexplored possibility. Avenues of cancer cell egress may include open bile and pancreatic ducts, transected positive resection margins, divided lymphatics and nerves or manual manipulation of the tumor. Previously reported, patients with negative pre-resection peritoneal washing cytology, who converted to positive cytology in postoperative drain fluid, had worse overall survival (Ann Surg 238(1): 103, 2003). Our objective was to perform a study of serial intraoperative cytologic washings to gain more direct evidence of PDA cell shedding during resection.

Methods: Patients undergoing surgical resection at one high volume pancreas center, Thomas Jefferson University Hospital, had intraoperative lavage fluid sampled by two conventional cytological assays (cytospin with Papanicolaou stain and cell block preparation with H&E stains). Additionally, we applied an epithelial immunohistochemical (IHC) marker that has been used for other tumor types, but rarely for PDA (BER-EP4 antibody). For each patient, three different washings were performed using 200 cc of lactated ringers: Washing 1, the pre-resection peritoneal washing immediately upon entering the abdomen; Washing 2, the post-resection peritoneal washing of the resection bed immediately after specimen removal; and Bucket Washing, performed ex-vivo in a small basin containing the specimen. The Bucket Washing provided proof of concept that shedding was a technical possibility. Association between positive cytology and clinicopathologic features was analyzed via Fisher's exact or chi-square tests.

Results: 45 patients underwent surgical resection (Whipple or distal pancreatectomy) for PDA. As shown in Table 1, immunolabeling with BER-EP4 increased the sensitivity of conventional cytological detection methods. In all cytological assays, the positive-cytology rate in the resection bed (Washing 2) was nearly twice the initial observed rate (Washing 1). Positive cytology in cytospin and cell block specimens obtained from the Bucket Washing correlated with positive resection margins ($p=0.0254$, $n=44$, and $p=0.0131$, $n=44$, respectively), and positive IHC from the resection bed (Washing 2) correlated with tumor size greater than 3.0 cm ($p=0.0279$, $n=37$).

Conclusion: These data provide the most direct evidence to date that PDA cells escape from the in situ surgical specimen during resection. Additional follow-up is required to determine whether positive cytology in the resection bed (Washing 2) predicts early recurrence and cancer-specific mortality. If so, high volume lavage to remove exfoliated cancer cells could improve outcomes.

Table 1. Positive cytology for each cytological method (n=45).

Wash #	Cytospin	Cell Block	IHC
1	3/44 (6.8%)	4/42 (9.5%)	7/43 (16.3%)
2	5/45 (11.1%)	7/43 (16.3%)	13/44 (29.5%)
Bucket	6/41 (14.6%)	15/43 (34.9%)	21/44 (47.7%)
Total	14/130 (10.8%)	26/128 (20.3%)	41/131 (31.3%)

42. EFFICACY AND FEASIBILITY OF COMBINING FOLFIRINOX AND STEREOTACTIC RADIOTHERAPY FOR PATIENTS WITH LAPC (LAPC-1 TRIAL)

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Background: Patients with locally advanced pancreatic cancer (LAPC) rarely undergo resection with curative intent and controlling disease progression should be the goal of the treatment. The first treatment of choice for locally advanced pancreatic cancer is systemic chemotherapy followed by subsequent local treatment. We conducted a multicenter phase II trial (ClinicalTrials.gov Identifier: NCT02292745) to investigate the efficacy and feasibility of combining FOLFIRINOX and Stereotactic Radiotherapy (SBRT) for patients with LAPC (LAPC-1 trial).

Methods: All eligible patients with biopsy-proven LAPC were included between January 2015 and June 2017. These patients underwent a staging laparoscopy to exclude occult metastasis and were treated with FOLFIRINOX (8 cycles) followed by SBRT (5 fractions/8 Gy) if there was no tumor progression on imaging. Primary outcome was overall survival (OS). Secondary outcomes were progression free survival (PFS), treatment-related toxicity, and resection rates.

Results: In total, 53 patients were included in the study. The preliminary survival data showed a median OS of 18 months (95% CI 16-19) and median PFS of 12 months (95% CI 11-13). Thirty (60%) events of a grade 3 or 4 adverse event occurred during FOLFIRINOX. Thirty-nine (74%) patients had no tumor progression after the chemotherapy and received the full dose of SBRT. One (3%) patient had a grade 5 adverse event three months after SBRT, while no grade 3 or 4 adverse event occurred after SBRT. Seven (14%) patients underwent a resection, all being a radical resection. Three (43%) had complete response in histopathological specimen examination, while the other four patients had moderate response.

Conclusion: FOLFIRINOX combined with SBRT in patients with inoperable LAPC is feasible and effective. Fourteen percent of the patients became resectable and 6% had a complete response.

43. FOLFIRINOX VS. GEMCITABINE/NAB-PACLITAXEL FOR NEOADJUVANT TREATMENT OF RESECTABLE AND BORDERLINE RESECTABLE PANCREATIC HEAD ADENOCARCINOMA: A PROPENSITY MATCHED ANALYSIS

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Background: Comparative effectiveness of FOLFIRINOX and Gemcitabine/nab-paclitaxel (G-nP) in the neoadjuvant treatment (NAT) of pancreatic ductal adenocarcinoma (PDA), remains unknown. The aim of this study was to perform a propensity matched analysis of neoadjuvant FOLFIRINOX vs G-nP for resectable(R) and borderline resectable (BR) PDA.

Methods: A single institution retrospective review of all R and BR PDA patients who underwent resection after NAT with FOLFIRINOX or G-nP was performed. Comparative effectiveness analysis was conducted using inverse-probability-weighted estimators. Primary endpoint was overall survival (OS) from the time of diagnosis.

Results: A total of 193 patients (FOLFIRINOX=73, G-nP=120) who underwent resection from 01/11-03/17 were included. Median OS was 28.9 months (95% CI 26.1-39.7). Patients treated with FOLFIRINOX were younger (median age 63 v 69 y), had less comorbidities (median CCI 4 v 5), more frequent BR disease (79 v 59%), and larger tumors (median CT size 2.9 v 2.7 cm) compared to G-nP (all $P < 0.05$). Both regimens were equally effective in achieving a 50% or 80% decline in CA19-9 (logistic regression, $P = 0.9$). Rates of R0 resection were also similar (80%), but folfirnox was associated with a reduction in pN1 disease (56% v 72%, $P = 0.028$). Receipt of adjuvant therapy was similar in both groups (74 v 75%, $P = 0.79$). In a multivariable cox regression analysis utilizing only preoperative variables (FOLFIRINOX v G-nP, age, gender, CT tumor size, BR vs R, pre NAT CA19-9 and number of NAT cycles), only the number of neoadjuvant cycles was an independent predictor of survival (HR 0.49, 95% CI 0.34-0.71, $P < 0.001$). In a propensity matched analysis of 166 patients using the same preoperative variables, the average treatment effect of FOLFIRINOX was to increase OS by 4.9 months above G-nP ($P = 0.012$).

Conclusion: FOLFIRINOX and G-nP are viable options for neoadjuvant treatment of PDA. In this study, FOLFIRINOX was associated with a 4.9 month improvement in OS when compared to G-nP in the neoadjuvant setting after adjusting for covariates.

44. SURVIVAL IN LOCALLY ADVANCED PANCREATIC CANCER: IMPACT OF SURGICAL RESECTION AFTER NEOADJUVANT THERAPY

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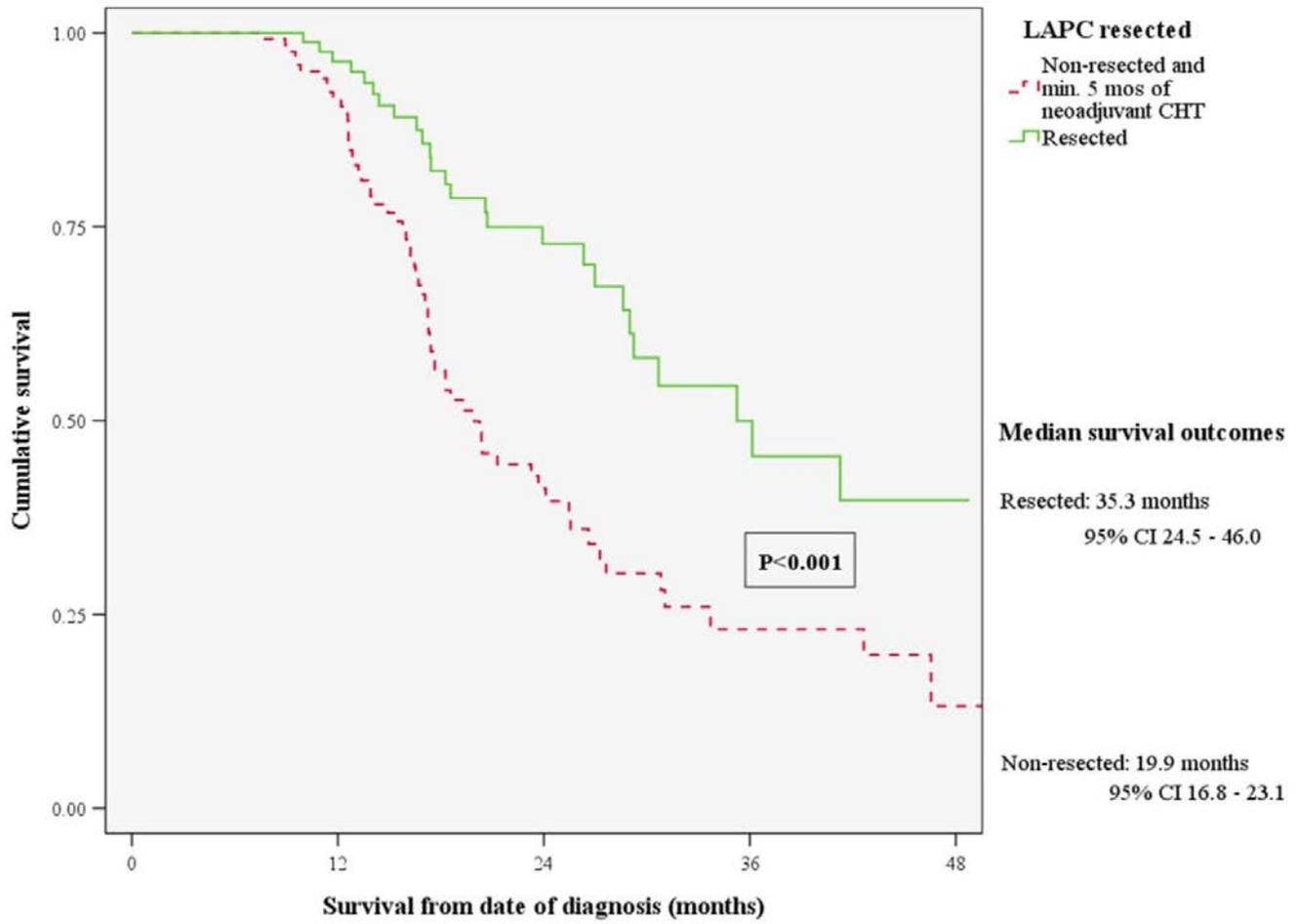
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Background: Current guidelines recommend systemic chemotherapy for locally advanced pancreatic cancer (LAPC). An increasing number of patients who respond favorably to neoadjuvant therapy undergo surgical resection of the primary tumor. The impact of surgery on patient survival is largely unknown.

Methods: This is a single institution retrospective cohort study that included all LAPC patients who presented to the Pancreatic Multidisciplinary Clinic (PMDC) of a high-volume pancreatic cancer center from January 1st, 2013 to September 30th, 2017. Demographics, and clinical data on neoadjuvant treatment and surgical resection were documented. Patients were stratified into two cohorts: surgical resection post neoadjuvant therapy, and systemic therapy only. Tumor resection rates, and overall survival (OS) were the primary study endpoints.

Results: Overall, 415 patients were included in the study. Significant heterogeneity was identified in neoadjuvant treatment. Stratification in FOLFIRINOX-based therapy, gemcitabine-based therapy, and combination of the two and subsequent outcome comparison did not demonstrate significant differences in OS of 331 non-resected LAPC patients (17.4 vs. 16 vs. 17.2 months respectively, $p=0.134$). Eighty-four patients underwent resection of the primary tumor (20%), after a median time of five months of neoadjuvant therapy. FOLFIRINOX-based therapy and stereotactic body radiation therapy (SBRT) correlated with increased probability of resection ($p=0.006$). Resected patients had better performance status, smaller tumor size (35 vs. 39mm, $p=0.029$), and lower median CA19-9 values (72 vs. 206U/ml, $p<0.001$). A significant improvement in OS was identified in resected patients, compared to non-resected (35.3 vs. 16.3 months, $p<0.001$). The difference remained significant when non-resected patients were matched for time of neoadjuvant therapy (19.9 months, $p<0.001$, Figure 1). Positive nodal status ($p=0.026$) and positive margin resection ($p=0.032$) correlated with shorter post-resection survival in the resected cohort.

Conclusion: Surgical resection of the primary tumor after neoadjuvant therapy is feasible in 20% of LAPC patients, and results to significantly higher OS, reaching a median time of 35 months from diagnosis.



No at. Risk

—	84	75	34	11	1
- - -	132	99	25	8	2

45. CLINICAL OUTCOMES AND LONG-TERM SURVIVAL ANALYSIS IN PATIENTS WITH LOCALIZED PANCREATIC DUCTAL ADENOCARCINOMA UNDERGOING CHEMORADIO THERAPY ACCORDING TO IAP INTERNATIONAL CONSENSUS ON THE DEFINITION OF BORDERLINE RESECTABLE CANCER 2017

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Background: Our institution has been performing chemoradiotherapy (CRT) for the patients with localized pancreatic ductal adenocarcinoma (PDAC). The aim was to evaluate clinical outcomes and long-term survival in the patients with CRT for localized PDAC according to IAP international consensus on borderline resectable cancer 2017 on the basis of three dimensions of anatomical (A), biological (B), and conditional (C) factors.

Methods: Among 307 consecutive patients pathologically diagnosed as localized PDAC who had been enrolled for our CRT protocol from February 2005 to December 2016, the subjects were 285 patients who could be re-evaluated after CRT. These 285 patients were classified according to international consensus A definition: R in 62, BR-PV in 27, BR-A in 50, LA in 146. Disease-specific survivals (DSS) were analyzed according to A factor, and furthermore B (CA19-9 and lymph node metastasis diagnosed by CT findings before CRT) and C factors (performance status: PS).

Results: The rates of resection and R0 resection were similar between R (83.9 and 98.0%) and BR-PV (85.2 and 95.5%), while those became much lower in BR-A (70.0 and 84.8%) and LA (46.6 and 62.5%). DSS evaluated by MST (median survival time, months) showed the data similar to surgical outcomes: 33.7 in R, 27.3 in BR-PV, 18.9 in BR-A and 19.3 in LA, respectively. DSS in R patients with CA 19-9 levels 500 U/ml or more was significantly poor than those with CA19-9 levels less than 500 U/ml, while there were no differences in DSS among BR-PV, BR-A and LA patients according to CA 19-9 levels (Figure). DSS in R patients with PS 2 or more was significantly poor than those with PS 0-1.

Conclusion: IAP international consensus on BR-PDAC on the basis of three dimensions of A, B, and C was proved to be useful and practicable because prognosis of PDAC patients is influenced by anatomical factors as well as biological and conditional factors, which in turn may help to make treatment strategy.

46. PERIOPERATIVE HYDROCORTISONE TREATMENT REDUCES POSTOPERATIVE PANCREATIC FISTULA AFTER DISTAL PANCREATECTOMY: A RANDOMIZED CONTROLLED TRIAL

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Background: Postoperative pancreatic fistula (POPF) is the major complication after distal pancreatectomy (DP) and the incidence remains high at 16-50%. In our recent RCT, we showed that perioperative hydrocortisone (HC) treatment reduces Clavien-Dindo 3-5 complications after pancreaticoduodenectomy (Laaninen et al, *Annals of Surgery* 2016). The aim of this study was to investigate whether perioperative hydrocortisone treatment reduces the risk for POPF after DP.

Methods: 40 patients planned for DP at Tampere University Hospital were randomized to receive perioperative treatment with intravenous HC 100 mg or placebo. The first dose was given at the induction of anaesthesia. 31 patients underwent DP and continued in the study. All had a high-risk, soft pancreas (>40% acini in the pancreatic transection line as analysed peroperatively). They continued to receive HC/placebo every 8 hours for two days postoperatively. All complications were graded, the primary endpoint being POPF.

Results: Median age was 68 (39-92) years, 35% were men. The groups were similar for age, sex, ASA class distribution and comorbidities. 90 days mortality was zero. All patients were determined as high-risk patients, having > 40 % acinar cells in the pancreatic transection line analyzed preoperatively. Pancreatic duct diameter, operative time and blood loss were similar between the groups. With HC treatment the rate of clinically significant POPF (grades B/C) were significantly reduced compared to placebo (5.9% vs 28.6%, $p=0.016$). The rate of overall Clavien -Dindo III-V complications were 5.9 and 21.4 % in the HC and placebo group, respectively (ns; $p=0.058$)

Conclusion: Perioperative hydrocortisone treatment reduces the clinically relevant fistula after distal pancreatectomy. HC may have a favorable effect even on overall major complications.

47. IDENTIFICATION OF RISK FACTORS FOR VENOUS THROMBOEMBOLISM IN PANCREATIC DUCTAL ADENOCARCINOMA PATIENTS UNDERGOING PRE-OPERATIVE CHEMOTHERAPY

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Background: Pancreatic ductal adenocarcinoma (PDA) is associated with a hypercoagulable state resulting in high risk of venous thromboembolism (VTE). VTE risk is well established for patients receiving chemotherapy for advanced disease and during the perioperative period for patients undergoing surgical resection. However, data is lacking for patients undergoing neoadjuvant treatment, who may have unique risk of VTE because of exposure to both the risks associated with chemotherapy and surgery.

Methods: Patients with PDA treated with neoadjuvant therapy followed by surgery were identified from pancreatic surgical databases from 2007 to June 2016. VTE including any venous thrombosis were evaluated from the start of treatment through the 90-day postoperative period. Risk factors including clinical factors, treatment variables and laboratory values evaluated prior to treatment and prior to surgery were assessed.

Results: 357 patients receiving neoadjuvant therapy prior to surgical resection were studied. Surgical resection included pancreaticoduodenectomy (76%), distal pancreatectomy (14%), distal pancreatectomy with celiac axis resection (DP-CAR, 9%), total pancreatectomy (<1%), and central pancreatectomy (<1%). 21% of patients had a VTE within 90 days postoperatively (n=75). VTEs (n=84) included PE (29%), DVT (31%), superficial vein thrombosis (5%), and thrombosis of the portal vein/SMV (35%), splenic vein (4%), and ovarian vein (1%). 73% of VTEs occurred during the postoperative period. Patients with VTE had significantly higher pretreatment neutrophil count, lower preoperative lymphocyte count, higher frequency of preoperative platelet/lymphocyte ratio >260, longer operative times and were more likely to receive radiation and undergo total pancreatectomy or DP-CAR. Age >65, pretreatment hemoglobin <10 g/dL and resection with DP-CAR or total pancreatectomy were independent predictors of VTE on multivariate analysis.

Conclusion: VTE during neoadjuvant treatment followed by surgery is common. Further study into novel thromboprophylaxis measures during neoadjuvant treatment and the perioperative period is warranted.

48. EVOLVING THE PARADIGM OF EARLY DRAIN REMOVAL FOLLOWING PANCREATODUODENECTOMY

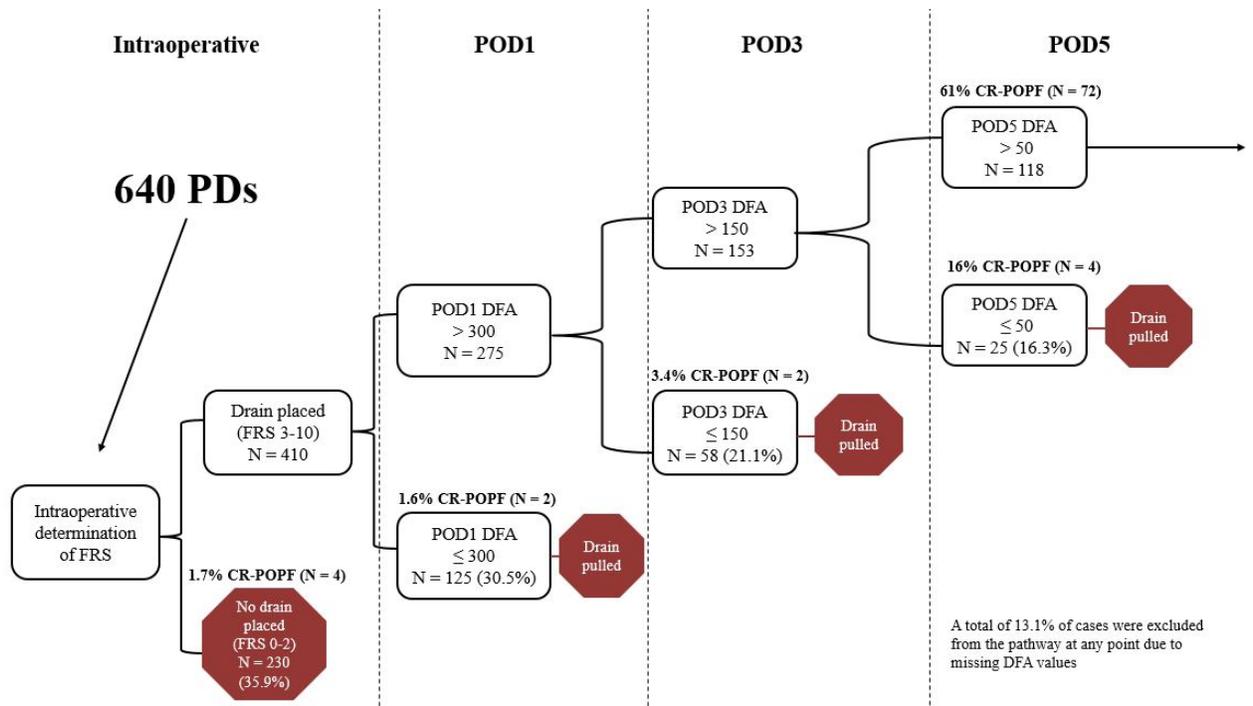
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Background: Recent data illustrates improved outcomes when adhering to selective and early removal of drains following pancreatoduodenectomy (PD). However, the mechanics underlying this paradigm, including selection of candidates, determinants of outcomes, and consensus of an “early” timeframe, remain nebulous. Given these challenges, this study aims to clarify the dynamic nature of the early drain removal concept.

Methods: 640 PDs, performed at two institutions (2014-17), were managed by a general policy of selective drain placement using the fistula risk score (FRS), paired with early removal based on a POD1 drain fluid amylase (DFA) threshold of 5000. Outcomes were reappraised in the framework of a novel proposal whereby intraoperative drain omission was utilized based on a low-risk profile (FRS 0-2), followed by drain removal sequentially at PODs 1, 3, & 5 if DFA fell below specific cutoffs based on optimized negative predictive values (NPV) for CR-POPF. Characteristics and outcomes of the ultimate cohort, enriched for CR-POPF risk, were analyzed using uni- and multivariable analyses (MVA).

Results: The overall CR-POPF rate was 15.2% (13.3% grade B; 1.9% grade C). Median DFA POD1, 3, & 5 were 440 (IQR 55-2977), 94 (20-518), and 150 (42-609), respectively. Intraoperative FRS calculation would preclude drains from 230 (35.9%) negligible/low risk cases with a resulting cohort CR-POPF rate of 1.7% (Fig 1). Of the remaining 410 patients, 30.5% would have drains removed on POD1 based on a DFA threshold of 300 (NPV=98.4%), demonstrating a 1.6% CR-POPF rate. Next, on POD3, drains could be removed in the residual cohort from 21.1% of patients whose DFA was \leq 150 (NPV=96.6%), reflecting a 3.4% CR-POPF rate. On POD5, a DFA threshold of 50 (NPV=84%) identified 16.3% more patients whose drains could be removed. The remaining “enriched” cohort (POD5 DFA $>$ 50), just 18.4% of the original patients, displays a 61% CR-POPF rate. This group has worse outcomes compared to patients with no drain or early drain removal, including severe complication (33.7% vs. 9.5%, $p < 0.001$) and length of stay (21 vs. 8 days, $p < 0.001$). Drains in the “enriched” cohort were removed on a median of POD9 (CR-POPF: 22 [8-34] vs. no CR-POPF: 6 [5-7], $p < 0.001$). On POD5, a DFA $>$ 2000 threshold best predicted subsequent CR-POPF (PPV=89.5%). MVA revealed a positive association between pancreatic cancer/pancreatitis and CR-POPF (OR=3.536, $p=0.034$). Overall, the ability to predict CR-POPF improved temporally across the sequence of management thresholds: intraoperative FRS (AUC=0.688), POD1 (AUC=0.791, $p < 0.001$), POD3 (AUC=0.841, $p < 0.001$), and POD5 (AUC=0.880, $p < 0.001$).

Conclusion: This data suggests a novel paradigm employing the principles of selective drain placement and early removal, which ultimately consolidates CR-POPF prediction. Furthermore, early drain removal is a fluid concept and can be employed throughout the postoperative time course using conditional thresholds.



49. CONTEMPORARY UTILIZATION OF AND OUTCOMES FOR EPIDURAL ANESTHESIA DURING DISTAL PANCREATECTOMY

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Background: Epidural analgesia (EA) is utilized for abdominal operations in an effort to decrease post-operative pain, minimize narcotic use, promote early mobilization and pulmonary toilet, and ultimately lead to fewer complications and shorter length of stay (LOS). The impact of EA for patients undergoing pancreatectomy has not been extensively studied.

Methods: Patients undergoing distal pancreatectomy (DP) were selected from the 2014 - 2016 ACS-NSQIP general and pancreatectomy-targeted datasets. Those having emergent procedures or concomitant hollow viscous, vascular, hepatic, or biliary resections were excluded. Patients receiving EA in conjunction with general anesthesia were compared to those with general anesthesia alone (non-EA). Post-operative outcomes including LOS, readmission, reoperation, 30-day mortality, and NSQIP captured complications were compared after stratifying according to operative approach (open, minimally-invasive DP [MIDP]) and performing propensity score matching (EA vs non-EA) for key covariates (age, sex, race, BMI, smoking, diabetes, hypertension, diagnosis, gland texture, duct size).

Results: 3372 DPs were identified, of which 452 (13.4%) received EA. At baseline, both groups were comparable with regard to age, gender, BMI, NSQIP measured comorbidities, and indication for resection. The most common diagnosis in each group was pancreatic adenocarcinoma (23.6% and 27.4%). EA use was significantly more common for open resections (71.2% vs 40.2%) compared to MIS (22.1% vs 44.4%) or MIS with open assist (6.7% vs 15.4%) ($p < 0.0001$). After propensity matching patients undergoing open DP, the only significant difference in peri-operative outcomes was a greater rate of DVT among EA vs non-EA patients (3.7% vs 0.6%, $p = 0.007$). For MIDP, rates of complications were found to be equivalent, however, even after propensity score matching, EA patients were found to have a significantly greater LOS (median 5 vs 4 days, $p < 0.001$).

Conclusion: Although EA is intended to result in fewer complications and shorter LOS, analysis of this large contemporary dataset of patients undergoing DP found otherwise. EA use is associated with greater rates of DVT for open DP and increased LOS following minimally-invasive DP. These results suggest EA supplementation to general anesthesia does not enhance outcomes following DP.

50. ROLLING OUT PANCREATIC ERAS: USING THE HAWTHORNE EFFECT AND "NEGOTIATION" PHASE TO GOOD EFFECT

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Background: Enhanced Recovery After Surgery (ERAS) protocols are emerging as an important tool in the delivery of efficient perioperative care, reducing hospital length of stay (LOS) without compromising outcomes. The objective of this study was to understand how the process of developing ERAS pathways for pancreatic resections itself influenced patient care at our institution.

Methods: Four surgeons worked closely with the hospital quality team to develop our own institutional ERAS pathways for pancreatic resections. At initiation of the project, the surgeons were given unblinded data regarding LOS and outcomes for all surgeons in the group. The patient cohort includes 300 patients who underwent isolated pancreatic resection between October 2015 and December 2017. Three time periods were examined: "Baseline" patients (n=136 patients over 13 months) who received traditional care; "Pathway Development" included patients from the initiation of the project (initial meeting between surgeons and hospital quality team to negotiate elements of pathway) until adoption (n=71 patients over 6 months); and "Pathway" were those enrolled in the formal ERAS pathway via a defined EMR order set after May 1, 2017 (n=93 over 8 months). LOS, complications, readmission, and mortality were evaluated among the groups.

Results: Three distinct ERAS pathways were developed: Whipple pancreaticoduodenectomy (target LOS 7 days), open distal pancreatectomy (target LOS 5 days) and laparoscopic distal pancreatectomy (target LOS 2 days). The process of developing the ERAS pathways itself reduced LOS, with a further reduction once the pathway rolled out formally after the "go-live" date (median LOS: Baseline (10.7 days) to Pathway Development (8.37 days) to Pathway (5.8 days) (p<0.005). This pattern held true for all three pathways individually (Table 1). ERAS implantation did not increase perioperative complications, 30-day readmission, or mortality. Renal, respiratory, cardiac, and superficial site infections all remained below NSQIP benchmarks.

Conclusion: Implementing an ERAS program for pancreatic resections contributed to a decreased LOS without compromising other outcomes. The significant reduction in LOS noted between Baseline and Pathway Development (prior to official pathway implementation) can be attributed to surgeon awareness of individual practice patterns and the collaborative discussions held between all specialties and care teams to create a consensus pathway to streamline care. The important impact of this period already demonstrated a marked reduction in LOS, which was sustained throughout the official ERAS pathway initiation.

Table 1 Length of stay for the individual pancreatic resection types.

Pancreatic Resection Type	Baseline	Pathway Development	Pathway
Whipple	13.01	9.81	6.9 (n = 55)
Open Distal Panc	8.38	6.60	5.2 (n = 24)
Lap Distal Panc	4.68	3.15	2.2 (n = 14)

51. DISCHARGE ON POSTOPERATIVE DAY #5 FOLLOWING PANCREATODUODENECTOMY: THE NEW GOLD STANDARD? - RESULTS OF THE PROSPECTIVE RANDOMIZED CONTROLLED WHIPPLE ACCELERATED RECOVERY PATHWAY (WARP) TRIAL

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Background: Standardized postoperative recovery pathways have proved effective in improving patient outcomes following complex surgery. This study was designed to determine whether an enhanced recovery pathway for pancreaticoduodenectomy (PD) could significantly reduce hospital length of stay (LOS) to 5 days without increasing complication or readmission rates.

Methods: PD patients (high risk patients excluded) were enrolled in an IRB approved, prospective, randomized controlled trial (NCT02517268) comparing a 5-day recovery pathway (WARP) to our traditional 7-day pathway (Control). WARP interventions included early discharge planning, shortened ICU stay, modified postoperative dietary and drain management algorithms, rigorous physical therapy with in-hospital gym visits, standardized rectal suppository administration, and close telehealth follow-up. The trial was powered to detect an increase in POD-5 discharge from 10% to 30% (80% power, $\alpha = 0.05$, two-sided Fisher's Exact test, target accrual 142 patients).

Results: Seventy-six patients (37 WARP, 39 Control) were randomized from June 2015 to September 2017. A planned interim analysis was conducted at 50% trial accrual resulting in mandatory early trial stoppage, as the predefined efficacy endpoint was met. Demographic variables between groups were similar (Table). The WARP significantly increased the number of patients discharged to home by POD-5 compared to Control (75.7% vs. 12.8%; $p < 0.001$) without increasing readmission rates (8.1% vs. 10.3%; $p = \text{NS}$). Complication rates were similar between the groups (27% vs. 43.6%; $p = 0.16$), with the exception of nasogastric tube replacement (13.5% vs. 41%; $p = 0.01$) and delayed gastric emptying which were reduced in the WARP arm (13.5% vs. 33%; $p = 0.059$). Inadequate oral intake prevented POD-5 discharge in the majority of Control patients (53.8%).

Conclusion: The WARP can safely reduce hospital LOS in PD patients without increasing readmission risk.

Table

	5-day (N=37)	7-day (N=39)	P-value
Gender	20 (54.1%)	18 (46.1%)	
Mean Age (years)	68.3 ± 20.2	67.3 ± 17.6	
Mean Body-Mass Index (kg/m²)	26.8 ± 4.3	26.1 ± 4.9	
Diabetes Mellitus	11 (29.7%)	11 (28.2%)	
History of Tobacco Use	15 (40.5%)	14 (35.8%)	
Pancreatic Ductal Adenocarcinoma Pathology	27 (73.0%)	30 (76.9%)	
Patients with Complication	10 (27.0%)	17 (43.6%)	0.16
Pancreatic Fistula	4 (10.8%)	2 (5.1%)	0.43
Delayed Gastric Emptying	5 (13.5%)	13 (33.0%)	0.059
Nasogastric Tube Replacement	5 (13.5%)	16 (41.0%)	0.010
POD 5 Discharge	28 (75.7%)	5 (12.8%)	<0.001
Readmission	3 (8.1%)	4 (10.3%)	1.0
30-Day Mortality	0 (0.0%)	0 (0.0%)	1.0

52. PROGNOSTIC NUTRITIONAL INDEX IS A STRONG PROGNOSTIC FACTOR IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA UNDERGOING CHEMORADIOTHERAPY FOLLOWED BY SURGERY

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Background: In variety of malignancies including pancreatic ductal adenocarcinoma (PDAC), not only tumor biological status but also conditional host-related immunonutritional status and systemic inflammatory response—such as prognostic nutritional index (PNI: $(10 \times \text{albumin}) + (0.005 \times \text{total lymphocyte counts})$), neutrophil lymphocyte ratio (NLR), Glasgow prognostic score (GPS) have been reported as prognostic factors. However, the influence of these factors on prognosis of PDAC patients who underwent chemoradiotherapy (CRT) followed by surgery remains unclear. The aim of this study is to evaluate influence of host-related immunonutritional status and systemic inflammatory response after completion of CRT on prognosis of PDAC patients.

Methods: Between February 2005 and May 2015, 235 consecutive PDAC patients underwent CRT using gemcitabine (GEM) or S1 plus GEM and followed up more than 2 years after initial treatment. Seventy four patients were excluded from this study, owing to incomplete CRT, insufficient laboratory data and CT. The remaining 161 patients were included in this study and we evaluated the post-CRT factors (at 1 month after completion of CRT) affecting disease specific survival.

Results: Among the 161 patients, 102 underwent curative-intent resection after CRT. In multivariate analysis, the significant post-CRT prognostic factors were PNI ($p=0.000004$), CRP ($p=0.008$), CEA ($p=0.0004$), RECIST classification ($p=0.0005$). Because post-CRT PNI was found to be most significant factor, its cut off value was determined by using cut-off finder as 39.0. Patients with PNI 39 or more ($n=131$) survived significantly longer than those with PNI less than 39 ($n=30$) (median survival time (MST): 21.3 months (M) vs. 9.2 M, $p<0.0001$). In patients with curative-intent resection ($n=102$), MST in patients with PNI 39 or more ($n=88$) was 25.4 M, which was significantly longer than 14.6 M in patients with PNI less than 39 ($n=14$), showing similar MST in patients without resection. When we divided 161 cases into three respectability groups according to the Japan Pancreas Society (JPS) classification: resectable (R, $n=39$), borderline resectable (BR, $n=39$), and locally advanced (LA, $n=83$), MSTs were significantly longer in patients with PNI 39 or more than in those with PNI less than 39 in each resectability group: 30.5 ($n=32$) vs. 14.5 M ($n=7$) in R, 17.6 ($n=36$) vs. 7.2 M ($n=3$) in BR, 20.3 ($n=63$) vs. 9.2 M ($n=20$) in LA.

Conclusion: PNI of 39 after CRT is a strong prognostic indicator for PDAC patients who underwent CRT followed by surgery regardless of tumor resectability. Even if the tumor is potentially resectable in anatomical aspect, we have to carefully make a decision of resection in patients whose PNI is less than 39.

53. 500 MINIMALLY INVASIVE ROBOTIC PANCREATICODUODENECTOMIES: ONE DECADE OF OPTIMIZING PERFORMANCE

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Background:

Background: Despite significant improvement in mortality for the pancreaticoduodenectomy over the past 4 decades, morbidity remains high. We sought to mitigate the high physiologic impact of this procedure by applying the minimally invasive approach utilizing the robotic platform.

Methods:

Methods: Retrospective review of a prospectively maintained database.

Results: Results: 500 consecutive robotic pancreaticoduodenectomy were performed between 2008 and 2017. Metrics of operative performance including conversion, blood loss, pancreatic fistula improved early in the experience and have remained low despite increasing complexity of case selection as reflected by increasing PDAC, vascular resections and higher CCIscores. Clavien 2> complications now occur in less than 24% of the patients. Clinically significant pancreatic fistula are observed in 7.8% of the patients and the 30- and 90-day mortality are 1.4 % and 3.1% respectively. Operating room time plateaued after 240 cases with a median time of 391minutes (IQR 340-477) for 500 cases. The median length of stay in the last 100 cases was 6 days and 74% percent of patients with pancreatic ductal adenocarcinoma received adjuvant chemotherapy.

Conclusion: Conclusions: Optimization of the robotic approach to the pancreaticoduodenectomy occurred rapidly over the last decade. These metrics establish a benchmark for the surgical community to consider in disseminating this approach.

54. REAPPRAISAL OF MAIN PANCREATIC DUCT IN IPMN UNDER SURVEILLANCE: DUCT DILATATION OF 5 TO 9 MM ALONE IS NOT ASSOCIATED WITH HIGH CANCER RISK

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Background: The correlation between the risk of pancreatic cancer (PC) and a dilated main pancreatic duct (MPD) in IPMNs is a matter of debate. The aim of this study was to assess the role of MPD size in predicting PC in a large cohort of both resected IPMNs and surveilled IPMNs.

Methods: All patients with a radiological or pathological diagnosis of IPMN referred to the The Pancreas Institute, University of Verona Hospital Trust, from 1985 to 2016 were included. The primary endpoint was the occurrence of PC detected at surgery or during follow-up.

Results: The final cohort consisted of 2134 patients, 439 resected and 1695 under surveillance, with a median follow-up of 67 and 43 months respectively. MPD dilatation was progressively associated with other features of malignancy, but when presenting alone, the occurrence of PC was 17%. For resected IPMNs, both an MPD measuring 5-9 mm or >10 mm were independent predictors of HGD or PC. Considering both resected and surveilled IPMNs, patients with an MPD between 5-9 mm had more than 10 years of survival without developing PC.

Conclusion: A MPD > 5 mm represents an independent predictor of PC in surgically resected IPMN. After including IPMNs under surveillance in the present analysis, the threshold to be an independent predictor of PC increased to >10 mm. In the absence of other features of malignancy, an MPD of 5 to 9 mm alone should not be considered as an absolute indication for surgical resection in presumed IPMNs.

	Univariate analysis			Multivariate analysis		
	Pancreatic Cancer		p	OR	CI95%	p
	No (n= 1440)	Yes (n= 167)				
Male sex	546 (37.9%)	85 (50.9%)	< 0.01	1.21	0.66 – 2.2	0.5
Age > 65	768 (53.4%)	110 (65.9%)	< 0.01	1.82	0.97 – 3.42	0.06
Diabetes	73 (15%)	39 (31%)	< 0.01	1.65	0.83 – 3.31	0.1
Symptoms	231 (17.8%)	74 (47.1%)	< 0.01	3.07	1.57 - 6	<0.01
Acute pancreatitis	135 (9.4%)	31 (18.6%)	< 0.01	2.33	1.05 – 5.16	0.03
Jaundice	12 (0.8%)	37 (22.2%)	< 0.01	15.24	4.83 – 48.14	< 0.01
Cyst's size > 30mm	200 (14.8%)	78 (56.9%)	< 0.01	2.88	1.59 – 5.23	< 0.01
Thickened walls (> 2mm)	32 (2.2%)	11 (6.6%)	< 0.01	1.36	0.36 - 5	0.6
Enhancing walls	20 (1.4%)	3 (1.8%)	0.4			
Mural nodules	63 (4.4%)	28 (16.8%)	< 0.01	0.93	0.43 – 5.23	0.8
MPD 5-9mm	160 (11.1%)	102 (61.1%)	< 0.01	1.72	0.99 – 6.72	0.07
MPD ≥10mm	35 (2.4%)	28 (16.8%)	< 0.01	17.13	6.06 – 48.41	<0.01

55. THE ROLE OF ABDOMINAL ULTRASOUND SCAN FOR THE FOLLOW-UP OF PANCREATIC CYSTIC LESIONS: A COST-SAVING AND SAFE ALTERNATIVE TO THE ROUTINE USE OF MRI?

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Background: Patients with pancreatic cystic lesions (PCL) without “worrisome features” (WF) at the time of diagnosis, usually necessitate a lifetime surveillance. According to the most recent international guidelines, follow-up should be performed with a MRI scan every 6 months in the first year, then annually for the next five years, in order to evaluate cysts size, appearance of pancreatic main duct dilatation or mural nodules. Since these parameters can also be evaluated with an ultrasound scan (US scan), we studied the safety, feasibility and economic impact of an abdominal US scan follow-up, with a delayed use of MRI.

Methods: We retrospectively evaluated the records of all the patients who had been followed-up with an abdominal US scan for the presence of “low risk” PCL in our institution. All of patients underwent to a US scan every six months for the first year and then, in case of stable disease, annually from the second to the fifth year. A surveillance MRI scan was routinely executed every two years, or according to the presence of considerable modifications at US. We compared the two methods regarding sensitivity and specificity in identifying cysts variations. We also focused on a costs-analysis between the theoretical application of the international guidelines follow-up with MRI, and our follow-up strategy with abdominal US scan and delayed MRI.

Results: Two-hundred patients were followed-up with abdominal US scan between January 2012 and January 2016 for PCL. One-hundred and forty-eight (69%) were females and 62 (31%) males. Mean follow-up period was 25.1 months (± 18.2). Surgery was required for 2 patients (1%), due to the appearance of WF at imaging (with concordance among US and MRI). During the follow-up, abdominal US showed “low grade” modifications in 28 patients (14%), comprising main pancreatic duct dilatation $< 6\text{mm}$ and increasing of the main cyst of about 0.5cm, compared to previous examinations. In all of these cases MRI confirmed US findings, without adding more prognostic information. In only 11 patients (5.5%) a routine MRI identified an evolution of the lesions, not showed at US, but only related to an increased number of the PCL ($p=0.14$). Nevertheless, a MRI every 6 months would not have changed in any case the decisional process. The mean cost of surveillance for each patient, in a theoretical application of international guidelines with MRI at our group of patients, should have been 402 ± 273.7 €, while according to our follow-up strategy it was 215.4 ± 212.6 €, - ($p < 0.0001$).

Conclusion: In patients with PCL without WF, abdominal US, could be a safe alternative to MRI, reducing the numbers of II level examinations and therefore reducing costs. Long term safety of this approach should be validated on a longer follow-up period, with a larger series of patients and prospective studies.

56. TRANSMEMBRANE MUCIN MUC13 DISTINGUISHES INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS FROM NON-MUCINOUS CYSTS AND IS ASSOCIATED WITH HIGH-RISK LESIONS

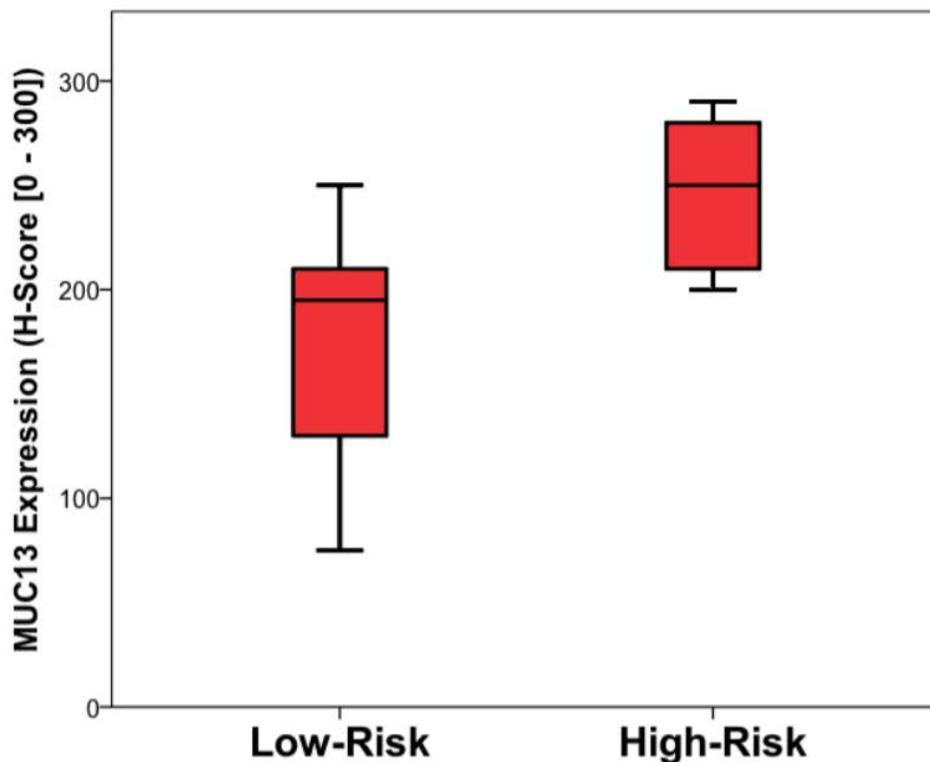
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Background: Intraductal papillary mucinous neoplasms (IPMN), a group of pancreatic cystic lesions with varying malignant potential, are currently managed based on imaging characteristics and results of cyst fluid sampling. The purpose of this study was to determine if MUC13, a glycoprotein aberrantly overexpressed in pancreatic adenocarcinoma, might aid in distinguishing high-risk lesions (high grade dysplasia [HGD] or invasive disease) from low-grade lesions.

Methods: Immunohistochemical staining for MUC13 was performed on formalin-fixed tissue specimens from 49 IPMNs and 23 non-mucinous cysts (16 SCA, 3 benign cysts, 4 chronic pancreatitis with pseudocyst) resected from 1998-2016. Membranous MUC13 expression was measured with the H-score, which quantifies the intensity of staining and the percentage of cells involved (range 0-300). MUC13 expression was compared using a Mann-Whitney U test among high-risk and low-risk IPMNs as well as in non-mucinous cysts (control).

Results: MUC13 expression was detected in 100% of IPMNs and was significantly greater than in non-mucinous cysts (median 220 vs 40, $p < 0.001$). MUC13 expression was similar among main ($n=26$), branch ($n=15$), and mixed ($n=8$) duct lesions (median 210, 210, 240, respectively). Amongst IPMN subtypes, the highest expression was observed in intestinal-type histology (median 275) and the lowest in gastric type (median 210). Of 49 IPMNs, 21 were high-risk (10 HGD, 11 invasive), and 28 had no more than low-grade dysplasia. MUC13 expression was significantly greater in high-risk lesions (median 270 vs 212.5, $p=0.031$). Among tumor characteristics, tumor size was also significantly associated with high-risk lesions (median 2.7 vs 1.7 cm, $p=0.029$).

Conclusion: MUC13 expression was significantly greater in high-risk IPMNs in this analysis. Assessment of MUC13 in cyst fluid samples warrants further investigation.



57. SURGICAL MANAGEMENT OF IPMN WITH MAIN DUCT INVOLVEMENT: AN INTERNATIONAL EXPERT SURVEY AND CASE-VIGNETTE STUDY

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Background: The risk of invasive cancer in resected intraductal papillary mucinous neoplasm (IPMN) with main pancreatic duct involvement is 33-60%. Most guidelines therefore advice resection of main duct (MD)-IPMN and mixed type (MT)-IPMN in surgically fit patients, although their advice on the surgical strategy (partial or total pancreatectomy) differs. We performed a survey amongst international experts to guide the design of future studies and guidelines.

Methods: An online survey including case-vignettes was sent to 221 international experts who had published on MD/MT-IPMN in the previous decade and to all surgeon and gastroenterologist members of the pancreatic cyst guideline committees of the European Study Group and the International Association of Pancreatology.

Results: Overall, 97 experts (67 surgeons, 30 gastroenterologists) from 19 countries replied; 44% response rate. Most (93%) worked in an academic hospital, with a median of 15 years' experience with IPMN treatment. In patients with MD/MT-IPMN and a dilatation > 5 mm of the entire pancreatic duct, 41%(n = 37) advised follow-up every 3-6 months, whereas 59%(n = 54) advised surgery. Of those who advised surgery, 46%(n = 25) would perform a total pancreatectomy and 31% (n = 17) pancreatoduodenectomy with follow-up. No structural difference in advise was seen between surgeons and gastroenterologists, between continents, and based on years of experience.

Conclusion: This international survey identified a clinically relevant lack of consensus in the surgical treatment strategy in MD/MT-IPMN among experts. Studies with long-term follow-up including quality of life after partial and total pancreatectomy for MD/MT-IPMN are required.

58. RISK OF MALIGNANCY IN MAIN-DUCT AND COMBINED-IPMNS IS STRONGLY ASSOCIATED WITH THE DEGREE OF MAIN PANCREATIC DUCT DILATION

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Background: In main duct (MD) or combined (CMD) IPMN pancreatic duct (MPD) diameter between 5-9 mm is identified by IAP guidelines as a worrisome feature (WF) requiring close follow up. However, some authors argue that the risk of degeneration in these patients is already high enough to recommend surgery. The aim of this study is to evaluate the significance of the MPD diameter at preoperative imaging as an independent predictor of high-grade dysplasia (HGD)/adenocarcinoma in MD-/CMD-IPMN.

Methods: Prospectively collected data was analyzed of patients undergoing pancreatic resection for IPMN at 3 high-volume pancreatic centers between 2009 and September 2017. MPD diameter was measured preoperatively with MRI, CT or EUS.

Results: 304 patients underwent pancreatic resection for IPMN. 263 had either a MD- (45 pts, 14.8%) or CMD-IPMN (218, 71.7%). Of these, 179 (68.1%) had HGD/carcinoma. This rate varied between patients with MD-IPMN (77.8%, 35 pts) and those with CMD-IPMN (66.4%, 144 pts) though not reaching statistical significance. Among the patients with HGD/carcinoma, 88.8% had at least one high-risk stigmata (HRS), 12.6% had at least one WF. Of the 98 patients with MPD >10 mm, 77.6% had degenerated IPMNs. A HGD/carcinoma was found in 81/122 (66.1%) patients with MPD 5-9 mm. However, 69 (85.2%) of these had at least one HRS and 10 had at least one other WF. Of the remaining 2 patients, one had elevated preoperative Ca19.9 and the other had only micro-foci of carcinoma at pathology. Thus, most patients with HGD/carcinoma would have had other indications for surgery beyond MPD 5-9 mm according to IAP guidelines. Considering only cases without other HRS, mean MPD diameter was 10.1 mm (2-60 mm) in case of HGD/carcinoma and 6.8 mm (2-11 mm) in benign IPMNs. ROC curve analysis identified 8.5 mm as the optimal cut-off in MPD diameter to distinguish low grade and high grade/invasive IPMNs (AUC 0.66). This cut-off was used in univariate analysis (OR 3.06, $p < 0.01$) with jaundice (OR 7.9, $p < 0.01$), the presence of nodules as an ordinal variable comprising non-enhancing (OR 1.1, $p 0.81$), enhancing (OR 4.2, $p < 0.01$) and macroscopic solid component (OR 5.8, $p < 0.01$), positive cytology (OR 14.8, $p < 0.01$), pancreatitis (OR 0.6, $p 0.11$), cyst ≥ 3 cm (OR 0.8, $p 0.51$), thickened wall (OR 0.6, $p 0.1$), abrupt MPD change (OR 1.7, $p 0.54$), elevated Ca19.9 (OR 5.2, $p < 0.01$) and altered glucose tolerance (OR 1.8, $p 0.17$). Multivariate analysis identified MPD ≥ 8.5 mm (OR 7.8, $p < 0.01$), enhancing nodules (OR 8.7, $p 0.01$), positive cytology (OR 12.2, $p < 0.01$) and elevated Ca19.9 (OR 3.37, $p 0.01$) as independent predictors of malignancy.

Conclusion: Our study confirms that, while for diameters ≥ 1 cm the risk of degeneration is high and surgical treatment must be recommended, smaller MPD diameters without other HRS do not appear to be as strongly linked to malignancy. A diameter of 8.5 mm was identified as the optimal cut-off with significant correlation to IPMN degeneration at multivariate analysis.

59. DEFINING THE ROLE OF LYMPHADENECTOMY FOR PANCREATIC NEUROENDOCRINE TUMORS: AN 8 INSTITUTION STUDY OF 695 PATIENTS FROM THE U.S. NEUROENDOCRINE TUMOR STUDY GROUP

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Emory University

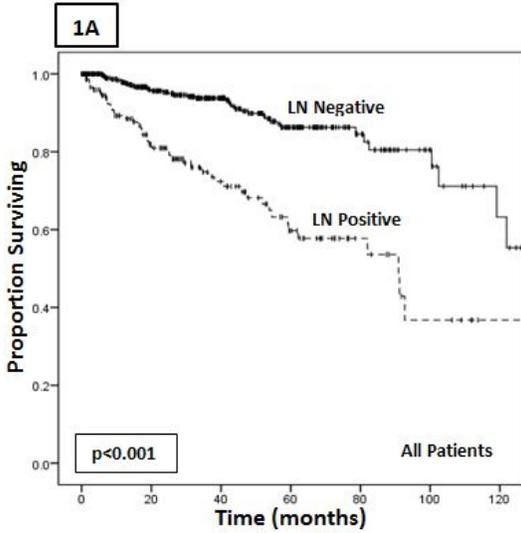
Background: Preoperative factors that reliably predict lymph node (LN) metastases in pancreatic neuroendocrine tumors (PanNETs) are unclear. The number of LNs needed to accurately stage PanNETs has not been defined.

Methods: Patients who underwent curative-intent resection of primary non-functional PanNETs at 8 institutions from 2000-2016 were analyzed. Tumors with poor differentiation and Ki-67>20% were excluded. Preoperative factors associated with LN metastases were identified. A procedure specific target for LN retrieval to accurately stage patients was determined.

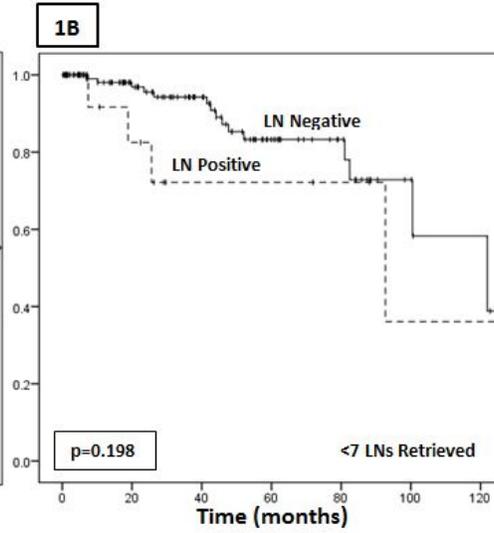
Results: Of 2182 patients with GI NETs, 695 underwent resection of PanNETs. 33% of tumors were proximal (head/uncinate), and 67% were distal (neck/body/tail). 26% of patients (n=158) had LN positive disease, which was associated with worse 5-yr recurrence-free survival (RFS) (60% vs 86%; $p<0.001$). Increasing number of positive LNs was not associated with worse RFS. Preoperative factors associated with LN positivity included tumor size >2 cm (OR 6.6; $p<0.001$), proximal location (OR 2.5; $p<0.001$), moderate vs well differentiation (OR 2.1; $p=0.006$), and Ki-67>3% (OR 3.1; $p<0.001$). LN metastases were also present in tumors without these risk factors: <2cm (9%), distal location (19%), well differentiated (23%), and Ki-67<3% (16%). Median LN retrieval was 13 for pancreatoduodenectomy (PD), but only 9 for distal pancreatectomy (DP). Given that PD routinely includes a complete regional lymphadenectomy, a minimum number of LNs to accurately stage patients was not identified. For DP, however, removal of <7 LNs failed to discriminate 5-yr RFS between LN positive and negative patients (<7 LNs: 72% vs 83%, $p=0.198$; >7 LNs: 67% vs 86%, $p=0.002$).

Conclusion: Tumor size >2 cm, proximal location, moderate differentiation, and Ki-67>3% are preoperative factors that predict LN positivity in resected non-functional PanNETs. Given the 9-23% incidence of LN metastases in patients without such risk factors, routine regional lymphadenectomy should be considered. Pancreatoduodenectomy inherently includes sufficient LN retrieval, while distal pancreatectomy should aim to remove >7 LNs for accurate staging.

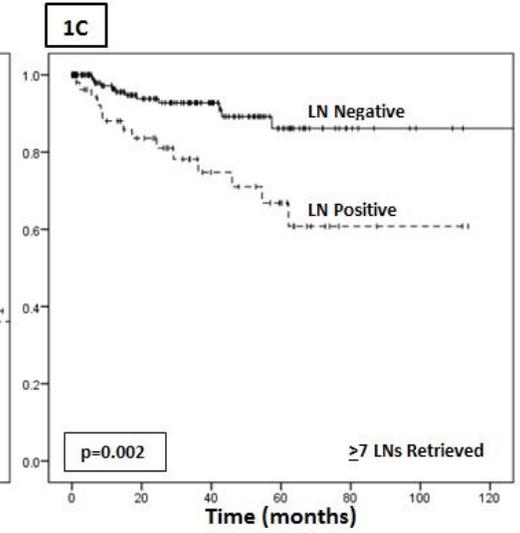
Recurrence-Free Survival



Recurrence-Free Survival		
LN Status	3-yr	5-yr
Negative	94%	86%
Positive	75%	60%



Recurrence-Free Survival		
LN Status	3-yr	5-yr
Negative	94%	83%
Positive	72%	72%



Recurrence-Free Survival		
LN Status	3-yr	5-yr
Negative	93%	86%
Positive	78%	67%

60. THE CONUNDRUM OF <2 CM PANCREATIC NEUROENDOCRINE TUMORS: A PREOPERATIVE RISK SCORE TO PREDICT LYMPH NODE METASTASES AND GUIDE SURGICAL MANAGEMENT

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Background: Management of <2 cm pancreatic neuroendocrine tumors (PanNETs) is controversial. Although often indolent, the oncologic heterogeneity of these tumors, particularly related to lymph node (LN) metastases, poses challenges when deciding between resection vs surveillance.

Methods: All patients who underwent curative-intent resection of primary non-functional <2 cm PanNETs at 8 institutions of the US Neuroendocrine Tumor Study Group from 2000-2016 were analyzed. Tumors with poor-differentiation and Ki-67>20% were excluded. Primary aim was to create a Lymph Node Risk Score (LNRS) that accurately predicted LN metastases for <2 cm PanNETS utilizing readily available preoperative data.

Results: Of 695 patients with resected PanNETs, 309 were <2 cm. 25% of tumors were proximal (head/uncinate), 23% had a Ki-67>3%, and only 8% were moderately-differentiated. 9% of all <2 cm tumors were LN positive, which was associated with worse 5-yr recurrence-free survival compared to LN negative disease (80% vs 96%; p=0.007). Preoperatively known factors associated with LN metastases were proximal location (OR4.0; p=0.002) and Ki-67>3% (OR2.7; p=0.05). Moderate-differentiation was not associated with LN positive disease. Location and Ki-67 were assigned a value weighted by their odds ratio: (distal: 1, proximal: 4; Ki-67<3%: 1, Ki-67>3%: 3), which formed a LNRS ranging from 1-7. Scores were categorized into low (1-2), intermediate (3-4), and high (5-7) risk groups. Incidence of LN metastases progressively increased based on risk group: Low: 3.2%; Intermediate: 13.8%; High: 20.5% (Table). Only 3.4% of Ki-67<3% tumors in the distal pancreas were LN positive compared to 21.4% of Ki-67>3% tumors in the head/uncinate.

Conclusion: This simple and novel LN risk score utilizes readily available preoperative factors (tumor location and Ki-67) to accurately stratify risk of LN metastases for <2 cm PanNETs and may help guide management strategy.

Lymph Node Positive Rates for <2cm PanNETs				
	Percent	p-value	OR (95%CI)	p-value
Lymph Node Risk Score		<0.001		
Low (Score 1-2) (n=195)	3.2%		Ref	--
Intermediate (Score 3-4) (n=61)	13.8%		4.9 (1.5-15.7)	0.007
High (Score 5-7) (n=53)	20.5%		7.9 (2.5-24.9)	<0.001

61. PATTERNS OF RECURRENCE AFTER RESECTION FOR PANCREATIC NEUROENDOCRINE TUMORS: WHO, WHEN, AND HOW?

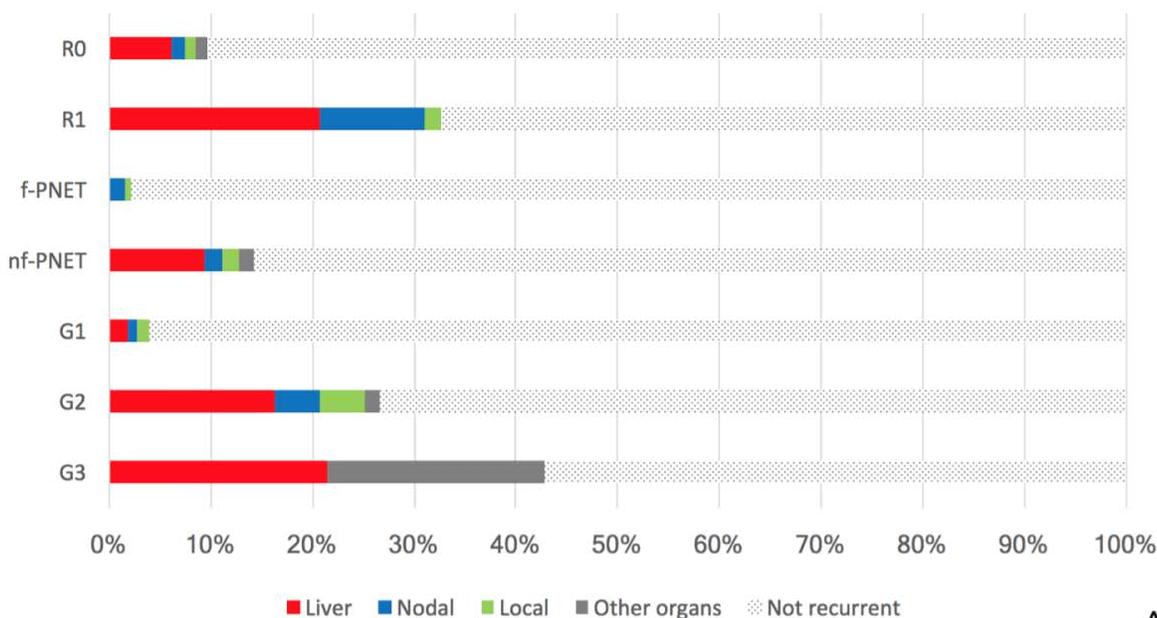
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Background: Pancreatic Neuroendocrine Tumors (pNETs) represent an increasing indication for pancreatic resection, but there are only few data about their possible recurrence after surgery. Aim of this study is to describe the frequency, timing, and patterns of recurrence after resection for pNETs with consequent implications for postoperative follow-up.

Methods: Retrospective analysis of pathologically confirmed pNET treated between 1990 and 2015 at the department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust. Predictors of recurrence were assessed by univariate and multivariate analysis. Survival analysis was conducted through the Kaplan-Maier and the conditional survival (CS) methods.

Results: The final cohort consisted of 487 patients with a median follow-up of 71 months. Recurrence developed in 12.3% of cases: 54 (11.1%) developed liver metastases, 11 (2.3%) local recurrence, 10 (2.1%) nodal recurrence and 8 (1.6%) metastases in other solid organs. Thirty-one (6.4%) died due to disease recurrence. Size > 20 mm, G3 grade, nodal metastasis and vascular infiltration were independent predictors of overall recurrence. Tumor recurrence occurred either in the first year after surgery (n= 9), and after ten years of follow-up (n= 4). CS analysis revealed that in case of a non-functioning G1 pNET <20mm without nodal metastasis and vascular invasion the risk of developing recurrence over time is negligible. Moreover, in the present series, after 5 years of follow-up without developing recurrence, tumor recurrence occurs only with liver metastases.

Conclusion: Recurrence of pNETs is rare and predicted by tumor size, nodal metastasis, grading and vascular invasion. Patients with G1 pNET without nodal metastasis or vascular invasion could be considered as cured by the surgery. After 5 years without recurrence, the follow-up should be focused in excluding the development of liver metastases.



62. INCIDENTAL HISTOLOGICAL DIAGNOSIS OF SMALL PANCREATIC NEUROENDOCRINE TUMORS: ARE WE UNDERESTIMATING THEIR INCIDENCE?

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Background: The annual incidence of pancreatic neuroendocrine tumors (PanNET) has been estimated to be around 0.8/100,000 inhabitants. Aim of the study was to determine the frequency of incidental histological diagnosis of PanNET during pancreatic specimen evaluation for other neoplasms.

Methods: We retrospectively reviewed 1023 histopathological examinations of pancreatic specimens performed by three different pathologists in 3 high-volume centers in Italy. Preoperative evaluations and surgical procedures were performed directly or under the supervision of a single surgeon. All the cases with a main pathological diagnosis of PanNET were excluded.

Results: An incidental associated diagnosis of PanNET was made in 38 specimens (4%). NET was the most frequent (57%) type of associated neoplasm followed by intraductal mucinous neoplasm (IPMN) (16%). Among those 38 cases, 29 (76%) had a largest diameter < 5 mm (microadenoma). 16 out of 38 incidental PanNET were classified as nonfunctioning (42%) whereas other 7 cases (18%) were classified as glucagonomas. A median value Ki67 of 1% was measured in 9 incidental PanNET. Patients with incidental PanNET were significantly older (median age: 69 years versus 65.5 years, $P=0.003$). There was no association between incidental diagnosis of PanNET and gender, operation, and main histological diagnosis. When excluding microadenomas, the median age between patients with incidental PanNET ($n=9$) and the remaining patients was not statistically different (median age 64 years versus 65.5 years, $P>0.05$).

Conclusion: The frequency of incidental histological diagnosis of PanNETs is considerably high suggesting that their real incidence is probably underestimated.

63. UTILIZATION OF PALLIATIVE CARE SERVICES AMONG PATIENTS WITH PANCREATIC CANCER

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Background: Early integration of palliative care (PC) services have been associated with lower hospital resource use and lower in-hospital deaths, particularly among patients with advanced or metastatic cancer. Herein, we describe statewide patterns of use of PC and clinical outcomes among patients diagnosed with pancreatic cancer.

Methods: Patients with primary pancreatic cancer were identified using the Maryland Health Services Cost Review Commission (HSCRC) database from 2013-2015. Hospital utilization and clinical outcomes were compared by receipt of PC.

Results: A total of 3,877 patients were identified who met inclusion criteria. PC services were utilized in 878 patients (22.6%) with four-fold higher utilization among patients who were management non-operatively compared with patients managed surgically (surgery vs. no surgery: 7.2% vs. 28.3%, odds ratio [OR] = 0.20, 95%CI: 0.15-0.25, $p < 0.001$). Among patients managed non-operatively, the median time to initiation of PC from diagnosis was 21 days (interquartile range [IQR]: 0-88), while that for surgical patients was 154 days (IQR: 25-350, $p < 0.001$). Among patients undergoing surgery, patients who received PC services were more likely to have developed a postoperative complication (palliative care vs. no palliative care: 44.0% vs. 26.5%, $p = 0.001$). Although 41% of patients who died received a PC consultation, median time from initiation of PC services to death was only 5 days (IQR: 2-15) among this sub-group of patients. Among patients discharged alive from their initial admission / visit, the median number of subsequent inpatient and / or outpatient visits was 4 visits (IQR: 2-9); receipt of PC services was associated with fewer subsequent inpatient and / or outpatient visits (incidence rate ratio [IRR] = 0.82, 95%CI: 0.80-0.84, $p < 0.001$).

Conclusion: Despite evidence of decreased hospital utilization with early initiation of PC, use of these services for pancreatic cancer remains low, particularly among surgical patients. PC services were initiated late in the course of management, either after failure-to-rescue or immediately prior to death. Future policies are required that encourage and incentivize early integration of PC into care practices.