1. NEOADJUVANT THERAPY AND THE PROLONGED RISK OF VENOUS THROMBOEMBOLISM IN RESECTABLE PANCREATIC CANCER

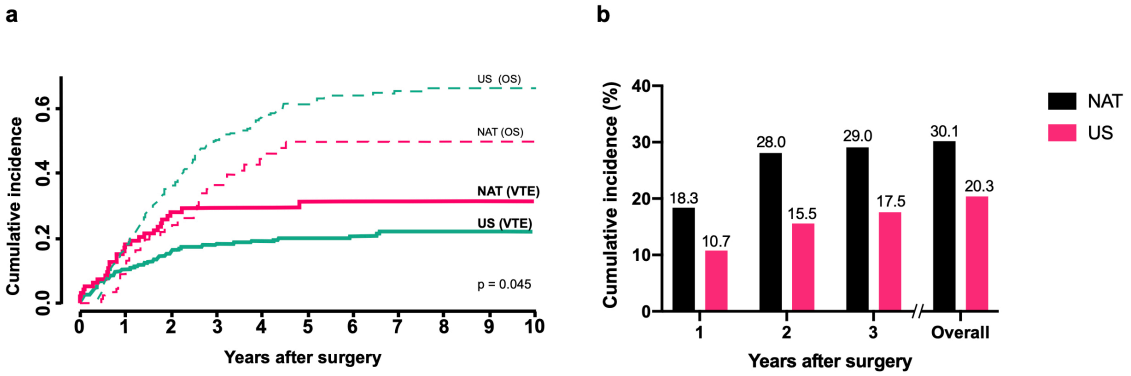
A Eurola, N Mattila, R Lassila, H Mustonen, C Haglund, H Seppänen
Presenter: Annika Eurola MD | Helsinki University Hospital, Finland

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most thrombogenic cancers and PDAC-patients are at 12-19% risk of venous thromboembolism (VTE). Chemotherapy is one of the risk factors for VTE. The purpose of this study was to investigate the relation between neoadjuvant treatment (NAT) and venous thromboembolism after surgery in PDAC. We also wanted to study the factors affecting on thromboembolism in the NAT group.

Methods: PDAC-patients surgically treated in Helsinki University Hospital 2006-2017 were identified (n=493). Following data was collected: venous thromboembolic events, BMI, age at surgery, neoadjuvant and adjuvant treatment, medication, resection marginal, tumor size, positive lymph node ratio, perivascular- and perineural invasion, surgical method, vascular reconstruction, and other cancers. The follow-up was at least 2 years or until death. Patients with another cancer (n=36), immediate death after surgery (n=5), stage IV and inoperable disease (n=54), lack of monitoring data (n=11), or coagulation disorders (Activated Protein C-resistance n=2) were excluded. One patient was operated twice and was included from the first operation. All diagnoses were histologically determined.

Results: 384 patients were analyzed. Overall incidence of VTE after surgery was higher in NAT patients compared to upfront surgery (US) patients (n = 28 (30.1%) vs. n = 59 (20.3% p = 0.049)). NAT was a statistically significant risk factor for VTE after surgery: HR 1.61 (95% CI 1.03-2.53 p = 0.037). In multivariate analysis of VTE NAT was a significant risk factor (HR 1.74 95% CI 1.07-2.81 p = 0.025). In overall survival (OS) analysis VTE was a statistically significant risk factor in both NAT (HR 3.25 95% CI 2.36-4.44 p 30 and disease recurrence.

Conclusion: Neoadjuvant therapy is an independent risk factor for venous thromboembolism after surgery in PDAC. In both the US and the NAT group, VTE is associated with increased mortality. Obesity, heart conditions and disease recurrence are associated with VTE.



NAT = neoadjuvant therapy US = upfront surgery VTE = venous thromboembolic event
OS = overall survival

2. A RANDOMIZED CONTROLLED TRIAL WITH INTRAOPERATIVE CYTOLOGIC SAMPLING FOR RESECTED PERIAMPULLARY ADENOCARCINOMA WITH IMPLICATIONS FOR LOCOREGIONAL RECURRENCE FREE SURVIVAL

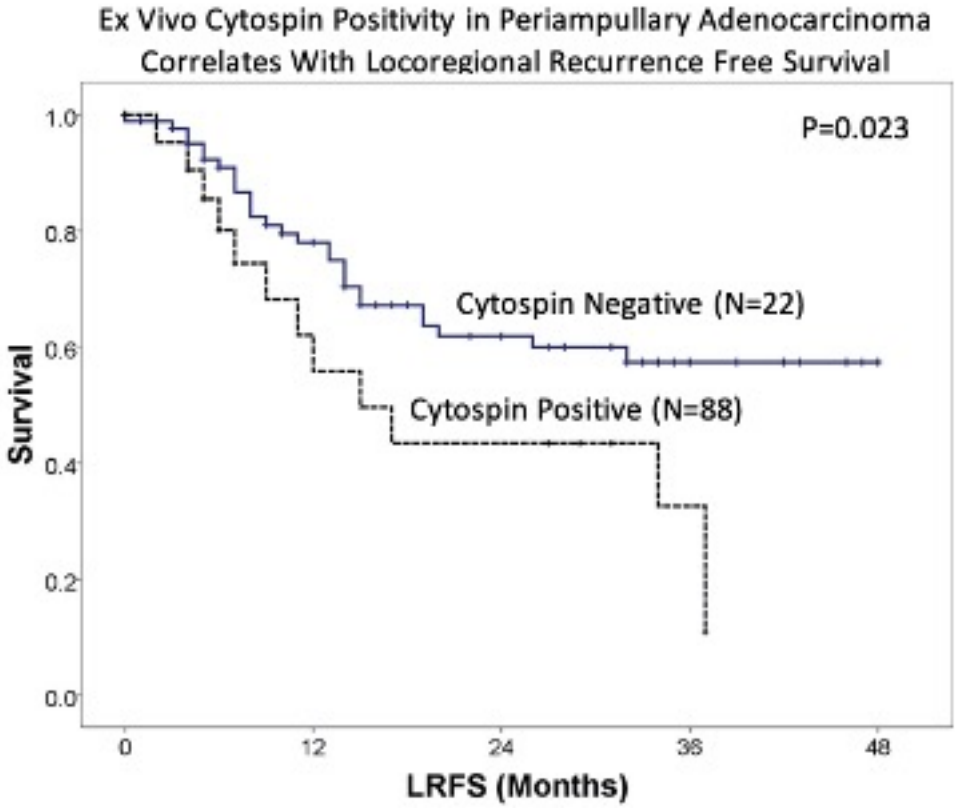
E Papai, A Nevler, C Solomides, M Shergill, T Yeo, S Cannaday, C Yeo, J Winter, H Lavu
Presenter: Emily Papai MD | Thomas Jefferson University, United States

Background: We hypothesize that PA recurrence after surgical resection may be affected by the shedding of malignant epithelial cells during surgical dissection and that this may have implications for disease recurrence and survival.

Methods: In this ongoing, investigator initiated prospective RCT, patients with PA were randomized intraoperatively, post-resection into 3 study arms: peritoneal lavage of 10L normal saline (NS) or distilled water (DW), or control group with no lavage. Peritoneal fluid was sampled for cytologic analysis (cytospin, cellblock, immunohistochemistry-Ber-EP4 antibody) at 4 stages: (I) abdominal entry pre-dissection, (II) resection bed following tumor extirpation, (III) ex-vivo resected specimen, and (IV) resection bed post-lavage.

Results: From 4/2016 to 5/2018, 167 PA patients were randomized. Prior to dissection (I) on cytospin analysis 4.9% were positive, which rose to 10.2% intraoperatively (II), 16.7% ex-vivo (III) and decreased to 4.3% (IV) after lavage. Lymph node metastasis, margin involvement, and perineural invasion did not correlate with locoregional recurrence (LR). Tumor cells in the ex-vivo cytospin (III) correlated with LR (OR 3.5, 95%CI 1.2-10.1, P < 0.05) and LRFS (P=0.02) (Figure). Cox regression analysis revealed tumor T-stage to have a HR 6.59 (0.90-48, P=0.06), and ex-vivo cytospin positivity to have a HR 1.98 (1.02-3.85, P=0.04) for LRFS.

Conclusion: Cytologic sampling from ex-vivo specimen irrigation after surgical resection of PA may have implications for LR, survival, and treatment, suggesting a possible cancer cell shedding phenotype.



3. INTRA-OPERATIVE BILE CULTURE IN PANCREATICODUODENECTOMY: TEACHING OLD DOGMA NEW TRICKS

TL Sutton, J O'Grady, R Martindale, SC Mayo, E Gilbert, BC Sheppard
Presenter: Thomas Sutton MD | Oregon Health & Science University, United States

Background: Biliary stents increase the risk of surgical site infections (SSI) following pancreaticoduodenectomy due to bactibilia and contaminated intra-operative bile spillage. Intra-operative bile culture (IOBC) is sometimes performed to guide postoperative antibiotic therapy for SSIs, however the utility of this practice is poorly studied. We sought to characterize the utility of IOBC and the interplay between stenting, bactibilia, and SSI following pancreaticoduodenectomy in a high-volume pancreatic cancer care center.

Methods: Patients undergoing pancreaticoduodenectomy from January 2008 to April 2020 were identified through our institutional National Surgical Quality Improvement Project (NSQIP) and cancer databases. Bile culture from the transected common bile duct were taken following stent removal, and IOBC results were collected; NSQIP-defined SSIs were analyzed with binomial logistic regression in a univariate a multivariate setting.

Results: Of 655 patients undergoing pancreaticoduodenectomy, 483 (74%) had IOBC and were included in the study; median patient age was 67 years. 189 (39%) patients had plastic stents, 154 (32%) had metal stents, and 140 (29%) were not stented. 329 (96%) patients with stents had bactibilia, compared to 18 (13%) without stents (P < 0.001). The biliary microbiome and antibiotic resistance patterns in patients with metal and plastic stents were nearly identical, but differed from patients without a biliary stent (Table).

Overall, 159 (33%) experienced an SSI, most commonly incisional (n=92, 22%). On multivariable regression controlling for relevant demographic, comorbidity, and operative characteristics, monomicrobial and polymicrobial bactibilia were independently associated with incisional SSI (OR 3.46 and 4.01, both P0.1). Stent type was not independently associated with odds of incisional or organ space SSI beyond associated bactibilia (P>0.5). Of 73 patients with speciated cultures from a SSI, 39 (53%) were polymicrobial; at least one organism identified from IOBC was present in 42 (58%), while at least one organism not identified on IOBC was present in 49 (67%).

Conclusion: Bactibilia is independently associated with incisional but not organ space SSI following pancreaticoduodenectomy and is strongly associated with stent presence. The decision for metal versus plastic stent placement should not be influenced by infectious concerns, as stent composition is not an independent risk factor for SSI and is not associated with unique biliary microbiomes or antibiotic resistance patterns. IOBC has a poor ability to predict causative organisms in SSI following pancreaticoduodenectomy, missing a causative organism in two-thirds of cases. IOBC is therefore not recommended for routine use.

Table: Heat Map of Intraoperative Bile Culture Results in Patients Undergoing Pancreaticoduodenectomy by Stent Type

Variable	Metal Stent N=154	Plastic Stent N=189	No Stent N=140	P Value
Positive Bile Culture	95%	97%	13%	<0.001
Polymicrobial	84%	85%	5%	<0.001
Organisms Identified†				
Enterococcus	46%	50%	11%	<0.01
Streptococcus	45%	48%	33%	0.50
Klebsiella	34%	33%	6%	<0.05
Enterobacter	25%	25%	11%	0.43
Escherichia coli	25%	19%	28%	0.33
Candida	14%	15%	0%	0.20
Clostridium	12%	12%	0%	0.31
Citrobacter	9%	5%	6%	0.35
Veillonella	9%	6%	6%	0.58
Bacteroides	6%	5%	6%	0.89
Lactobacillus	6%	4%	6%	0.76
Pseudomonas	3%	2%	0%	0.61
Antibiotic Resistance Pattern*				
BLR	33%	30%	50%	0.36
Single Agent Resistance (Non-BLR)	17%	23%	8%	0.32
Multi-Drug Resistance	10%	11%	0%	0.25

†Percent of Positive Cultures

*For n=206 with sensitivities measured (n=90 metal stent, n=104 plastic stent, n=12 no stent)

Abbreviations: BLR=Beta-lactam resistant

4. THE IMPORTANCE OF TIME TO INITIAL TREATMENT IN PATIENTS WITH PANCREATIC ADENOCARCINOMA

K Sugumar, S Gendi, HA Quereshy, JJ Hue, S Gupta, LD Rothermel, LM Ocuin, JB Ammori, JM Hardacre, JM Winter

Presenter: Kavin Sugumar MD | Case Western Reserve University School of Medicine, United States

Background: Currently, there are no guidelines regarding an appropriate time from diagnosis to first treatment among patients with pancreatic adenocarcinoma (PDAC), given its aggressive nature. Herein, we aim to define the average time-to-treatment in PDAC, factors associated with delay, and prognostic significance

Methods: We conducted a retrospective study of patients evaluated for PDAC at our institution (2017-2020). All stages were included. Patient demographics and various healthcare parameters were recorded. We sub-divided time-to-treatment (in days) into four categories: (i) T1: Time from symptom onset to initial provider evaluation, (ii) T2: Time from initial provider evaluation to tissue diagnosis, (iii) T3: Time from diagnosis to treating specialist consultation, (iv) T4: Time from specialist visit to first treatment, (v) and overall duration or time to treatment (TTT, T1+2+3+4).

Results: 217 patients met inclusion criteria. The median T1, T2, T3, T4 was 30, 7, 4, and 14 days respectively (Table 1). Patients presenting with weight loss (β =108.6, p=0.002) had greater T1. More frequent hospitalization (β =19.5, p0.05).

Conclusion: It takes a median time of less than a month for a patient with PDAC to start treatment once they visit a primary provider. This should be the bar, however 50% of patients exceed this standard and 25% of patients take longer than 50 days. Various patient and healthcare parameters can identify patients at risk for treatment delay. The greatest opportunity to shorten overall TTT is by having patients seek medical attention earlier (T1).

Table 1. Time-to-treatment (days).

Time duration (days)	Mean	10^{th} percentile	25^{th} percentile	50^{th} percentile	75^{th} percentile	90^{th} percentile
T_1	65.86	1	10	30	60	140
T_2	17.09	1	1	7	17	45
T_3	14.26	0	1	4	13	40
T_4	17.44	5	9	14	22	34
T_{2+3+4}	57.31	21	29	45	66	115
$T_{1+2+3+4}$	111.76	22	45	70	138	233

5. PRE-OPERATIVE POSITRON EMISSION TOMOGRAPHY PREDICTS POST-NEOADJUVANT CHEMOTHERAPY PATHOLOGICAL TREATMENT RESPONSE AND SURVIVAL IN BORDERLINE-LOCALLY ADVANCED PANCREATIC DUCTAL ADENOCARCINOMA

A Abdelrahman, J Yonkus, R Alva-Ruiz, M Kendrick, D Nagorney, S Cleary, R Smoot, T Grotz, A. Goenka, M Truty

Presenter: Amro Abdelrahman MBBS, MS | Mayo Clinic, United States

Background: Neoadjuvant chemotherapy (NAC) is utilized in patients with borderline/locally advanced (BR/LA) pancreatic ductal adenocarcinoma (PDAC) prior to consideration of resection. Major pathologic treatment response after NAC is among the most significant independent factors of survival, however only known post-resection. Conventional anatomical imaging (CT/MRI) is poorly predictive of treatment response and biochemical (CA19-9) markers are not useful in a significant proportion of patients. Functional metabolic imaging (FGD PET) may provide insight into tumor viability and survival after NAC. This study aimed to evaluate post-NAC PET in predicting pathologic response and subsequent survival in patients with BR/LA PDAC undergoing resection.

Methods: We retrospectively analyzed all BR/LA PDAC patients undergoing resection after NAC that underwent PET scan within 60 days of resection. Metabolic (PET) response was graded (FDG uptake compared to background) and dichotomized (Major vs. Minor). Pathologic treatment response (PR) was graded and dichotomized (Major vs. Minor). Biochemical response (CA19-9) was assessed before and after NAC and dichotomized (Optimal vs. Suboptimal). Pre- and postoperative factors associated with survival were assessed. Metabolic (FDG PET) and biochemical (CA19-9) responses were compared to final pathologic treatment response using sensitivity, specificity, likelihood ratios (LR+, LR-), and post-test probability of major PR.

Results: All patients had at least 1 FDG PET scan prior to resection with 182 (90.1%) having 2 or more FDG PET scans pre-operatively during the neoadjuvant phase. PET imaging modality was PET/CT in 35 (17%) or PET/MRI in 167 (83%) with 122 (60%) of patients having FDG PET scan prior to any treatment with a mean (median) SUV of 6.5 (6.1) with only 4 (3.3%) patients with treatment naïve non-avid tumors. Major metabolic response after NAC and prior to resection was present in 104 (52%) of patients. Of those patients with CA19-9 elevation at diagnosis, 71 (53%) normalized their levels after NAC. There were 140 (74.1%) patients alive at last follow-up with median recurrence-free and overall survival of 29.2 and 48.7 months respectively. Major pathologic response was seen in 77 (38%) patients and was the single largest 'postoperative' predictor of both RFS and OS on multivariable analysis. Of those with major pathologic response, 93.1% had correlative major metabolic response that strongly correlated with major PR (0.67, $p<0.01$) with 0.93 sensitivity and 0.81 specificity (LR+=4.95, LR-=0.09). Biochemical (CA19-9) response weakly correlated with PR (0.35, $p<0.01$) with 0.81 sensitivity and 0.59 specificity (LR+=1.96, LR-=0.3). Major metabolic response was the single largest 'preoperative' predictor of OS and RFS on multivariable analysis.

Conclusion: Among resected BR/LA PDAC patients who received NAC, preoperative FDG-PET predicts pathologic treatment response and survival after resection. Given the poor ability of standard imaging modalities or biochemical markers to assess NAC responses, functional FDG-PET imaging may provide significant insight into the efficacy of NAC to support either moving forward with surgical resection or consideration of NAC alterations. Larger prospective studies are warranted and currently ongoing to examine the role of functional imaging (FDG PET) in BR/LA PDAC treatment response assessment.

6. THE CLINICAL IMPACT OF CA19-9 NORMALIZATION FOLLOWING NEOADJUVANT THERAPY IN PANCREATIC CANCER: A MULTI-INSTITUTIONAL STUDY

A Hammad, M Zenati, S AlMasri, A Paniccia MD, K Lee MD, N Bahary, A Desilva, M Aldakkak, D Evans, S Tsai, A Zureikat

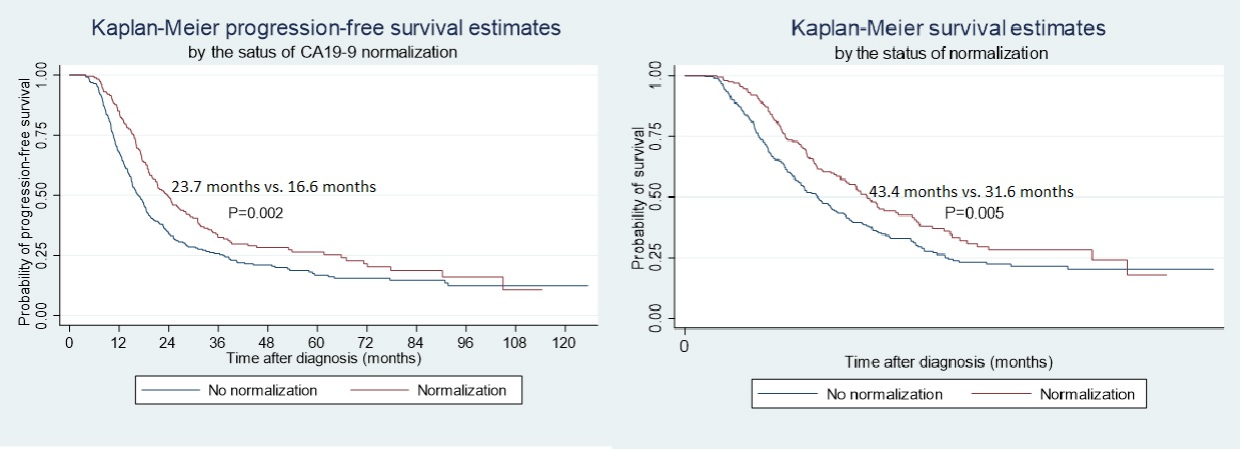
Presenter: Abdulrahman Hammad MBBCh | University of Pittsburgh Medical Center, United States

Background: Carbohydrate antigen 19-9 (CA19-9) is the most clinically useful biomarker for the diagnosis and management of pancreatic cancer (PC). Data on the significance of normalization of the CA19-9 level following neoadjuvant therapy (NAT) are seldom reported. We sought to examine the implications of CA19-9 normalization during NAT on overall survival (OS).

Methods: Patients who underwent surgical resection following NAT between 2010-2018 were retrospectively reviewed and those who had an elevated CA19-9 data correlating with total bilirubin of < 2 U/mL on pre-NAT laboratory investigations were included. Normalization was defined as a post-NAT CA19-9 level of < 37 IU/ml. Kaplan-Meier survival estimates, and Cox-proportion hazard regression were performed to identify predictors of survival.

Results: Four hundred and fifty patients were included (mean age 65, 50% females). Normalization was observed in 42% of the cohort (n=190). Normalization was associated with more NAT cycles (3 vs. 2, p<0.001) and receipt of neoadjuvant radiation (61% vs. 47%, p=0.001). Normalizers were found to have smaller pathologic tumor size (2.4 vs. 3.0 cm), higher incidence of lymph node negative disease (59%vs. 39%), negative surgical margins (78% vs 64%) and less frequent perineural or lymph-vascular invasion (62% vs.82% and 38% vs. 57% respectively) (all p<0.05). Normalization was associated with an improved PFS (24 vs 17 months, p=0.002, Figure) and OS on Kaplan-Meier estimates (43 vs 32 months, p=0.005, Figure). On multivariate analysis examining factors associated with survival, an interaction between CA19-9 normalization and receipt of 4 or more cycles of NAT was associated with better PFS [HR: 0.64 (0.42, 0.98), p=0.042] and OS [HR: 0.62 (0.40, 0.94), p=0.027].

Conclusion: In this multi-institutional analysis, we demonstrate that CA19-9 normalization following NAT is a significant prognostic indicator in surgically resected PC. CA19-9 normalization may serve as a useful endpoint when assessing NAT efficacy, particularly in association with 4 or more cycles of NAT.



7. ELEVATED POSTOPERATIVE CA19-9 IN PATIENTS WITH PANCREATIC CANCER FOLLOWING THE COMPLETION OF NEOADJUVANT THERAPY AND SURGERY – IMPLICATIONS FOR ADJUVANT THERAPY AND SURVEILLANCE

EP Ward, KK Christians, M Kamgar, B George, M Griffin, B Hunt, P Chisholm, WA Hall, BA Erickson, DB Evans, S Tsai

Presenter: Erin Ward MD | Medical College of Wisconsin, United States

Background: Carbohydrate antigen 19-9 (CA19-9) is an important prognostic marker in pancreatic cancer (PC). Although normalization of CA19-9 has been associated with improved survival, approximately one-third of patients who complete neoadjuvant therapy and surgery will have an elevated postoperative (postop) CA19-9. We evaluated the characteristics of patients with elevated postop CA19-9 values and their oncologic outcomes.

Methods: Consecutive patients with operable PC and an elevated CA19-9 at diagnosis (total bilirubin /=35) and obtained at the first postop re-staging evaluation approximately 6-10 weeks after surgery. Progression-free survival (PFS) and overall survival (OS) from the date of diagnosis were analyzed.

Results: In total, 236 patients were identified; postop CA19-9 was normal in 156 (66%) patients and elevated in 80 (34%). Among the 156 patients with a normal postop CA19-9, the median postop CA19-9 was 14 (IQR:11), compared to 80 (IQR:95) for the patients with an elevated postop CA19-9. There were no differences in demographics, clinical stage, tumor size, median CA19-9 at diagnosis, or receipt of adjuvant therapy between groups. Comparing additional outcomes in those with and without a normal postop CA19-9 we found the following differences: margin positive (R1) resections, 13 (8%) of 156 vs 19 (24%) of 80 (p=0.001); N2 disease (>4 positive nodes), 11 (7%) of 156 vs 14 (18%) of 80 (p=0.05); disease recurrence, 80 (51%) of 156 vs 56 (70%) of 80 (p=0.006); early recurrence (< 12 months), 39 (25%) of 156 vs 46 (57%) of 80 (p<0.001). The median PFS was 24 months for all 236 patients; 35 months for the 156 with a normal postop CA19-9 and 15 months for the 80 patients with an elevated postop CA19-9 (p<0.001). Metastatic disease was the first site of recurrence in 67 (43%) of the patients who normalized and 53 (66%) of the patients who did not (p=0.003). The median OS was 38 months for all 236 patients; 46 months for the 156 patients with a normal postop CA19-9 and 22 months for the 80 patients with an elevated postop CA19-9 (p<0.001). In an adjusted hazards model, an elevated postop CA19-9 was associated with an increased risk of death (HR:2.14, 95%CI 1.51-3.04, p= < 0.001) and adjuvant therapy was associated with a decreased risk of death (HR:0.71; 95%CI:0.50-0.99, p=0.04).

Conclusion: Elevated postop CA19-9 after neoadjuvant therapy and surgery is associated adverse pathologic features including R1 resection and N2 disease. Patients with elevated postop CA19-9 are at extremely high risk of disease progression within 1 year of surgery and should be monitored closely. Adjuvant therapy may be beneficial for patients with an elevated postop CA19-9 following neoadjuvant therapy and surgery, a perfect population for clinical trial enrollment.

8. THE SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) PREDICTS NEOADJUVANT THERAPY RESPONSE AND SURVIVAL IN PATIENTS WITH PANCREATIC CANCER WHO ARE CA 19-9 NON-SECRETORS

P Murthy, M Zenati, S AlMasri, A DeSilva, N Bahary, A Singhi, S Ellsworth, A Paniccia, K Lee, M Lotze, A Zureikat

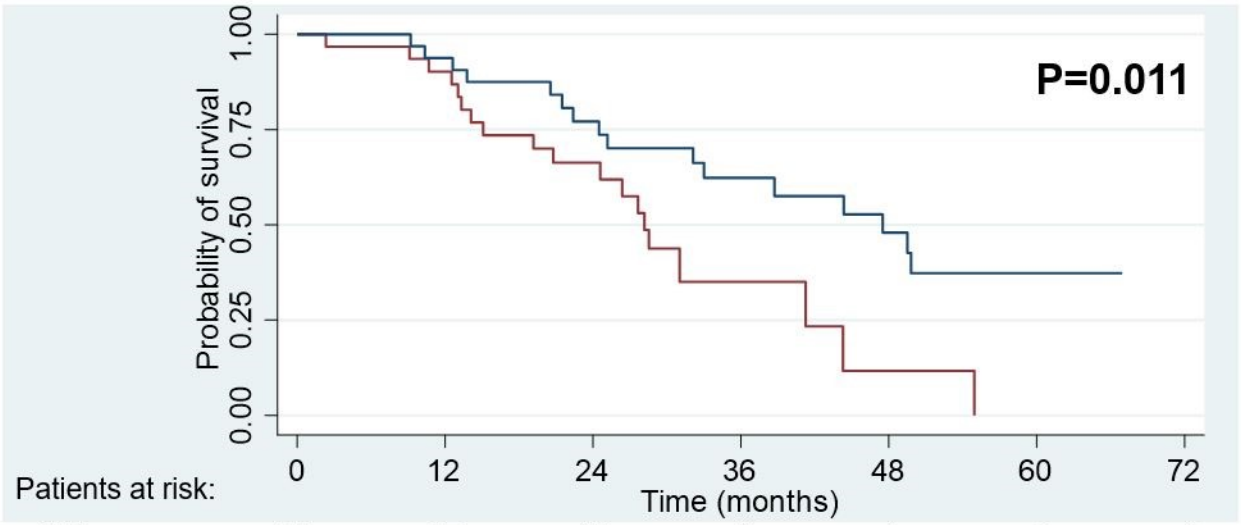
Presenter: Pranav Murthy MS | University of Pittsburgh Medical Center, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) is an inflammatory cancer characterized by heightened autophagy and a tolerogenic immune response. The aggressive, systemic nature of PDAC, along with improvements in chemotherapeutic regimens has warranted the increasing utilization of neoadjuvant therapy (NAT) for patients with localized disease. Given the fibrotic nature of PDAC, radiographic indicators are not precise predictors of outcome; however, reduction in serum carbohydrate antigen 19-9 (CA 19-9) after NAT is a surrogate for predicting treatment response and survival. Unfortunately, patients with a negative Lewis antigen phenotype (up to 34%) do not present with an elevated CA 19-9 and represent a significant population in need of dependable biomarkers of outcome. We recently identified the systemic immune-inflammation index (SII: absolute platelet count x (absolute neutrophils / absolute lymphocytes)) as a negative prognostic indicator of survival in patients with resectable PDAC undergoing NAT that is also associated with a CA 19-9 response. We examined the prognostic utility of SII in patients with localized PDAC undergoing NAT who are CA 19-9 non-secretors.

Methods: This retrospective study reviewed all PDAC patients presenting with normal CA 19-9 levels (CA 19-9 < 37 U/mL at diagnosis and total bilirubin < 2.0 mg/dL) treated with NAT prior to pancreatic resection at a single institution between 2014 – 2020. Pre- and post-NAT complete blood count and differential lab values were collected within 14 days of diagnosis and surgery to calculate SII (absolute platelet count x (absolute neutrophils / absolute lymphocytes)).

Results: Of 351 patients treated, 77 (22%) CA 19-9 non-secretors were identified with a median follow-up of 45.8 months. Mean age was 63.9 years, 48% were female, 52% received Gemcitabine/Abraxane, 74% underwent Whipple surgery, and 50% achieved margin negative resection. Although CA 19-9 levels did decrease following NAT (median (IQR): 12 (2.1, 26) to 5.1 (2, 13.8), p=0.0002), neither a 50% (p=0.98) nor 80% (p=0.54) decrease was associated with overall survival. Similarly, pathologic response, as determined by CAP score or Evans grade did not correlate with overall survival (p=0.185). Although patients who experienced a reduction in SII were more likely to have a BMI < 30 (p=0.045), no other differences were observed among perioperative variables. Patients who experienced any reduction in SII after NAT had both improved progression free (median PFS 28.7 months, 95 CI [12.66, 21.4] vs 15.72 months [20.55,37.78]; p=0.017) and overall survival (median OS 47.5 months, [31.12, not reached] vs 28.1 months [20.78, 41.26]; p=0.011). An increase in SII was an independent negative predictor of progression free (HR 3.92 [1.68, 9.15], p=0.002) and overall survival (HR 8.72 [2.46, 30.88], p=0.001).

Conclusion: In CA 19-9 non secretors, the SII response can predict progression free and overall survival in patients receiving neoadjuvant therapy prior to surgical extirpation of the tumor. An SII reduction during NAT may serve as one of the few determinants of chemotherapy response in this patient population and its utility as a biomarker warrants further investigation.



Group	SII Increase	SII Decrease
N	31	32
Median OS	28.1	47.5
[95 CI]	[20.78, 41.26]	[32.12, unreached]

9. GOAL-DIRECTED NEOADJUVANT TREATMENT OF OPERABLE PANCREATIC CANCER: ACHIEVING CA19-9 RESPONSE TO CHEMOTHERAPY PRIOR TO SURGERY

SZ Thalji, M Aldakkak, KK Christians, CN Clarke, B George, M Kamgar, BA Erickson, WA Hall, A Khan, P Tolat, T Giorgadze, DB Evans, S Tsai

Presenter: Sam Thalji MD | Medical College of Wisconsin, United States

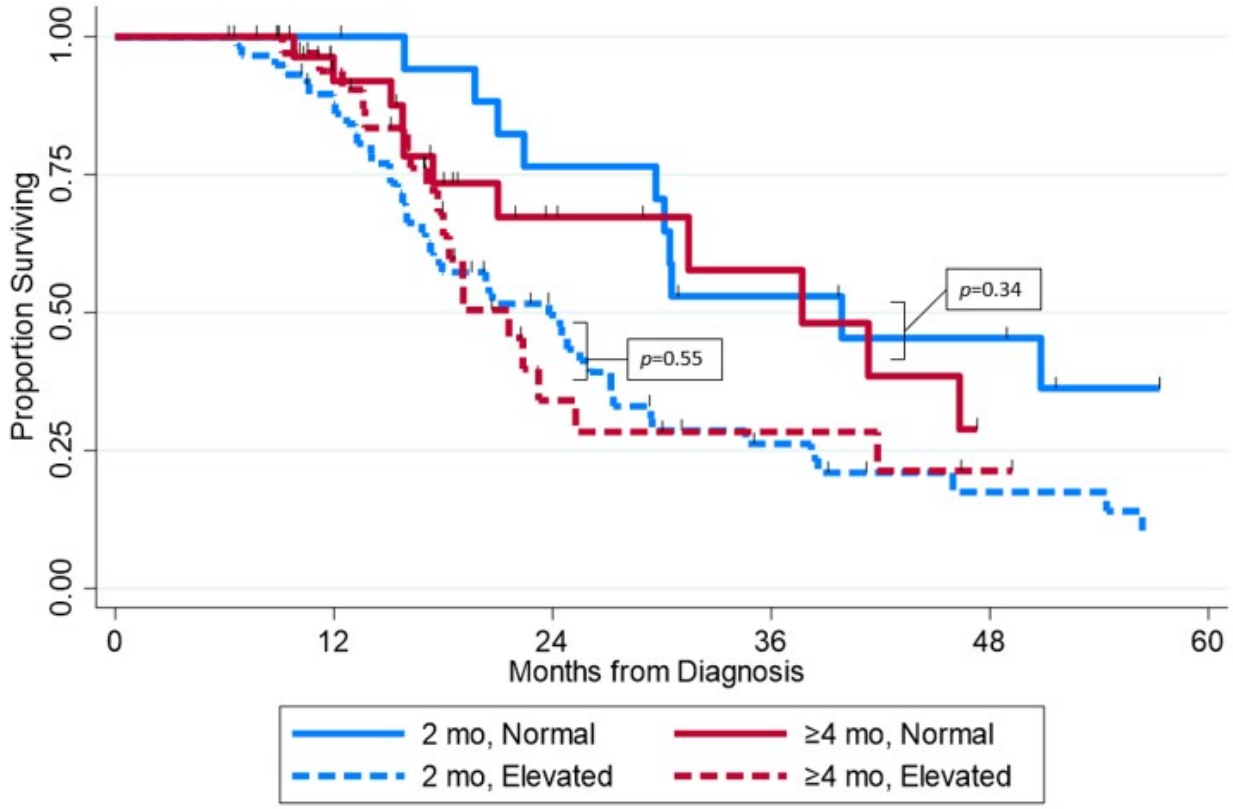
Background: The optimal length of neoadjuvant chemotherapy for patients with operable pancreatic cancer (PC) is controversial. We compared the effect of length of chemotherapy on carbohydrate antigen 19-9 (CA19-9) response and median overall survival (mOS).

Methods: We studied all patients with operable PC and an elevated CA19-9 at diagnosis (total bilirubin 35 U/ml) and assessed at the following time points: diagnosis (CA199dx); the end of chemotherapy (CA199chemo); and following XRT prior to surgery (CA199preop). Proportional change in CA19-9 was calculated as (CA199chemo – CA199dx) / CA199dx. Response was defined as a ≥50% decline from CA199dx.

Results: Of all 150 patients, 81 (54%) received 2 mo and 69 (46%) received ≥4 mo of chemotherapy. Of the 150 patients, 100 (67%) received FOLFIRINOX, 30 (20%) received gemcitabine/nab-paclitaxel, and 20 (13%) patients initially received FOLFIRINOX before being switched to gemcitabine/nab-paclitaxel due to lack of response. Following completion of all chemotherapy, CA199chemo response was observed in 35 (43%) of the 81 patients who received 2 mo of chemotherapy, compared to 56 (81%) of the 69 patients who received ≥4 mo ($p<0.001$). In adjusted logistic regression, patients who received ≥4 mo of therapy had a 6.25 increased odds of having a CA199chemo response ($p<0.001$). CA199chemo normalized in 18 (22%) of the 81 patients who received 2 mo and 29 (42%) of the 69 patients who received ≥4 mo ($p=0.009$). Of the 150 patients, 107 (71%) completed all intended neoadjuvant therapy and surgery; 75 (82%) of the 91 patients who experienced a CA199chemo response and 32 (54%) of 59 patients without a CA199chemo response ($p<0.001$). The mOS of all 150 patients was 25 mo; 30 mo for the 91 patients with a CA199chemo response and 21 mo for the 59 patients without a CA199chemo response ($p=0.005$). The mOS of patients with a normal CA199chemo who received 2 or ≥4 mo of chemotherapy were 40 mo and 38 mo, respectively ($p=0.34$) (Figure 1, solid lines). The mOS of patients with an elevated CA199chemo who received 2 and ≥4 mo of chemotherapy, were 21 mo and 19 mo, respectively ($p=0.55$) (Figure 1, dotted lines). On multivariate analysis, a CA199chemo response (HR:0.40, $p=0.001$) or CA199chemo normalization (HR:0.44, $p=0.002$) were each associated with improved OS.

Conclusion: There is an urgent need to define thresholds of response for neoadjuvant therapy. Once patients achieve normalization of CA19-9 with chemotherapy, it may be reasonable to progress to the next treatment modality. However, treatments cannot be continued indefinitely, and achieving a ≥50% decline in CA19-9 with neoadjuvant chemotherapy may be a clinically important threshold. Establishing meaningful biologic thresholds for optimal treatment sequencing will facilitate a goal-directed approach to neoadjuvant therapy and further studies should validate these endpoints.

Figure 1: Overall Survival by Chemotherapy Length and CA19-9 Normalization



10. THE EFFECT OF NEOADJUVANT THERAPY ON IMMUNE PROFILING OF PANCREATIC DUCTAL ADENOCARCINOMA: A PROSPECTIVE STUDY OF THE REOPANC-1 RANDOMIZED CONTROLLED TRIAL

D Latifi, W de Koning, S Lau, F Grevers, C van Dam, CHJ van Eijck, and DAM Mustafa on behalf of the Dutch Pancreatic Cancer group

Presenter: Dana Mustafa MD | Erasmus University Medical Center, Netherlands

Background: The randomized phase III trial (PREOPANC-1) that was performed in 16 centers in the Netherlands compared the effects of preoperative chemoradiotherapy (Gemcitabine and 2.4 Gy radiation) versus immediate surgery for resectable and borderline resectable pancreatic cancer. The outcomes of the secondary endpoints and predefined subgroup analyses suggest an advantage of the neoadjuvant approach. The aim of the present study was to investigate the changes in the immune microenvironment and infiltration caused by the neoadjuvant treatment.

Methods: To that aim, we collected formalin-fixed, paraffin-embedded pancreatic cancer samples from all centers that participated in the PREOPANC -1 trial. We performed targeted gene expression using the PanCancer Immune Profiling panel of NanoString.

Results: Comparing 50 samples of the patient who were subjected to neoadjuvant treatment to 46 treatment-naïve samples showed a distinct genetic profile induced by the neoadjuvant therapy. More than 250 immune-related genes were significantly differentially expressed between the two groups of samples. The results indicate that neoadjuvant therapy resets the innate immune activation in the tissue samples. A significantly higher infiltration of CD14+, CD33+, CSF1R+, and CD163+, MRC1+ cells were found in samples of the neoadjuvant arm. In contrast, B and various subtypes of T cells like CD8+ and FOXP3+ T cells showed a significant decrease in samples of the neoadjuvant arm. Pathway analysis revealed that the neoadjuvant treatment stimulated the expression of genes related to complement activation, chemotaxis, and wound repair while genes related to lymphocyte activation and adaptive immune responses were dominant in the treatment-naïve arm.

Conclusion: In conclusion, this is the first comprehensive study to describe the immune-molecular changes as a result of neoadjuvant therapy in a randomized clinical trial. The results reveal the enrichment of the myeloid compartment following neoadjuvant therapy which was significantly associated with a survival benefit for the patients. Studying the personalized effect of neoadjuvant therapy will guide choosing the appropriate combined therapy for pancreatic cancer.

11. ROLE OF PORTAL BLOOD CSF1R/IL-8 SIGNALING IN PANCREATIC CANCER CIRCULATING TUMOR CELL SURVIVAL

A Rosales, S Whisner, M Srivastava, N Fanaian, SA Litherland, JP Arnoletti
Presenter: Armando Rosales MD | AdventHealth Cancer Institute, United States

Background: The portal venous circulation provides a conduit for pancreatic ductal adenocarcinoma (PDAC) tumor cells to reach liver parenchyma sinusoids, a frequent target of metastatic deposits. Portal vein turbulent flow allows for retention of tumor-shed circulating tumor cells (CTC) and myeloid-derived immunosuppressor cells (MDSC). The chemokine interleukin-8 (IL-8) attracts myeloid cells via their CXCR2 receptors. CSF2 (GM-CSF) signaling through its receptor CSF2R promotes CSF1R expression on myeloid cells. Interleukin-34 (IL-34) and/or macrophage colony-stimulating factor (M-CSF/CSF1) signal through CSF1R promotes both myeloid cell differentiation to MDSC and myeloid-derived fibroblasts (M-FB). The ability of CTC to use these myeloid signaling pathways could allow CTC to use M-FB to aid in their survival in the portal blood.

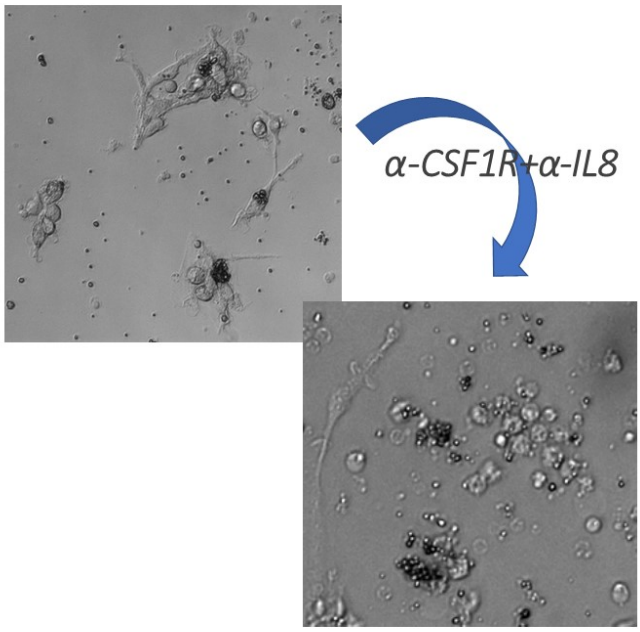
Methods: We collected portal venous blood from 26 PDAC patients undergoing pancreatico-duodenectomy. CD44+, CD147+, EPCAM+/CK+, CD45- CTC and CD14+, CD105+, CD45+ M-FB candidate cells were FACS isolated as single cells and in vivo formed clusters for use in ex vivo CTC/M-FB cultures for proliferation, biomarker, gene expression, and cluster formation analyses. To test the importance of myeloid attraction and signaling to CTC survival in the portal blood, humanized monoclonal blocking antibodies to CSF1R (BMS-986227, Cabralizumab), IL-8 (BMS-986253), and mouse monoclonal antibodies to IL-34 (1D12, Abcam) were used to inhibit CTC/M-FB signaling pathways.

Results: Portal blood CTC and M-FB interaction promoted multi-cellular cluster formation, promoting CTC proliferation over CTC alone (p=0.0245). Both CTC and M-FB expressed CSF1R, CSF2R, and CXCR2 receptors. PDAC portal blood had significantly higher levels of GM-CSF, M-CSF, IL-8, and IL-34 than peripheral blood controls. CTC expressed IL-34, CSF1, CSF2 and IL-8 RNA. Anti-IL-8 & anti-CSF1R together or IL-34 alone blocked CSF2R/CSF1R/CXCR2 signaling in CTC but not in M-FB. Inhibition of IL-8 & CSF1R or IL-34 induced IL-8 expression in M-FB, increased CTC apoptosis, and prevented CTC/M-FB cluster formation. IL-34 RNA expression persisted in both CTC and M-FB, even in the presence of IL-8 and CSF1R inhibition.

Blocking IL-34 function but not CSF1R alone prevented conditioned media from promoting differentiation of U937 myeloid precursor cells towards more anti-tumor myeloid cell differentiation (M□/DC). Combined anti-IL-34/anti-CSF1R/anti-IL8 inhibition also blocked M□/DC differentiation, but allowed M-FB differentiation to continue.

Conclusion: Blocking IL-8 signaling from CTC allowed myeloid cells to produce their own IL-8 and avoid being drawn to CTC and their CSF1/IL-34/CSF2 influence on myeloid differentiation. Without myeloid cell attraction and differentiation, clusters don't form, leaving CTC unaided by M-FB, and myeloid cells differentiating away from immunosuppressive, pro-tumor phenotypes. Such treatments could lead to enhanced anti-tumor myeloid cell responses and suppression of CTC survival.

Our data suggest that PDAC CTC form clusters with M-FB in the portal circulation and that interaction is dependent on autocrine and paracrine signaling mechanisms mediated by CSF1R and IL-8, with IL-34 signaling playing an important role in M-FB differentiation. Portal blood PDAC CTC/M-FB interactions via CSF1R, IL-8, and Il-34 signaling may be a potential target for therapeutic intervention.


α-CSF1R+α-IL8

12. SELECTIVE TARGETING OF A FLUORESCENT ANTIBODY TO MUCIN-5AC WHICH BRIGHTLY VISUALIZES A LIVER METASTASIS OF PANCREATIC CANCER IN A PATIENT DERIVED ORTHOTOPIC XENOGRAFT MOUSE MODEL

S Amirfakhri, H Nishino, N Neel, BM Clary, S Kaur, K Mallya, RM Hoffman, SK Batra, M Bouvet
Presenter: Michael Turner MD | Academic Medical Center, United States

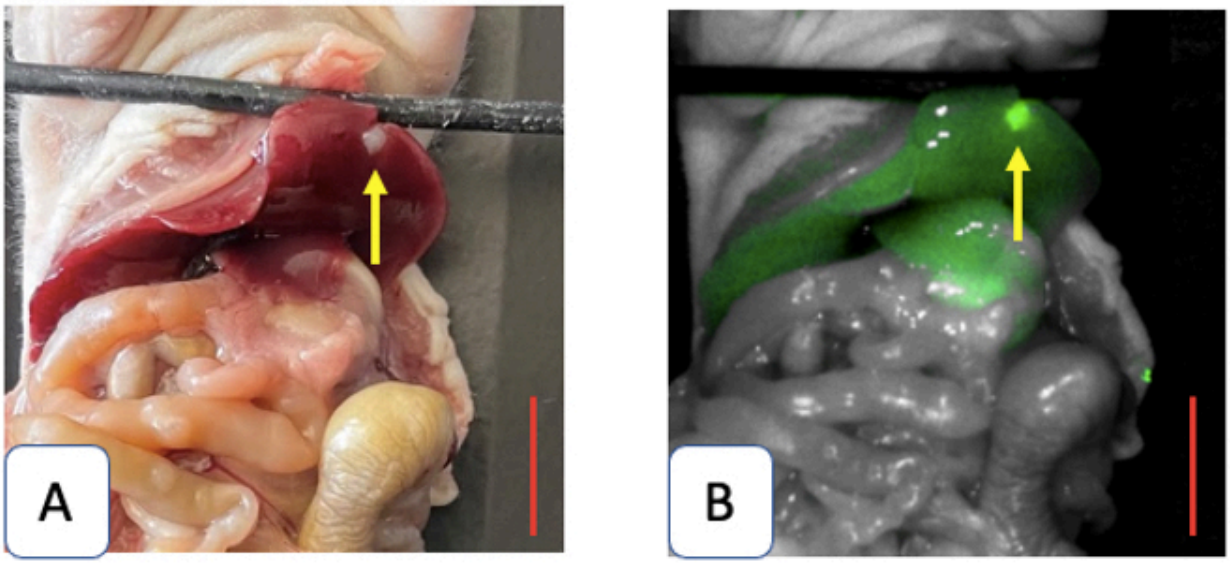
Background: Pancreatic cancer is one of the leading causes of cancer-related mortality in the United States with a five year-survival rate of 10%. The majority of patients with pancreatic cancer are not surgical candidates due to unresectable disease or metastatic spread, most often to the liver. Up to 35% of patients are found to have metastatic disease during staging laparoscopy. The need for imaging modalities to identify small metastatic disease is required to improve visualization and direct appropriate treatment. Mucins are a class of glycoproteins that play a role barrier protection and cellular signaling. They are overexpressed in certain cancers, such as pancreatic cancer, making them an attractive molecular target. Our laboratory has previously shown the utility of fluorescent antibodies for tumor detection in various cancers and in fluorescent guided surgery (FGS) which reduced rates of recurrence of disease and extended survival in orthotopic nude mice. In the present study, the use of a fluorescently-labeled mucin-5AC antibody (MUC5AC) preferentially targets pancreatic cancer in an orthotopic mouse model.

Methods: A MUC5AC monoclonal antibody was conjugated to the infrared dye IRDye800CW (LICOR, Lincoln, NE) to synthesize MUC5AC-IR800. A high MUC5AC expressing patient-derived metastatic pancreatic tumor from the liver (Panc Met) was previously obtained via surgical resection. Liver orthotopic implantation in nude mice was performed with 1 mm^3 Panc Met fragments, previously grown in subcutaneous models. After 3 weeks of PDOX tumor growth, 50 mcg of MUC5AC-IR800 was administered via tail vein injection and 72 hours later, in-vivo imaging was performed with the Pearl Trilogy Imager (LICOR, Lincoln, NE) with excitement at 800 nm. Tumor to background ratios (TBR) were calculated in the subcutaneous model using skin as background. In the orthotopic model, liver was used as background to calculate TBR.

Results: Western blotting demonstrated no MUC5AC expression in normal pancreatic tissue and MUC5AC overexpression in the Panc Met tumor. The subcutaneous Panc Met models demonstrated greatest tumor to background ratio (TBR) 72 hours after injection with 50 mcg of MUC5AC-IR800. In the liver orthotopic model, 72 hours after IV administration of MUC5AC-IR800 50 mcg, the mean TBR in the liver orthotopic model was 1.817 (SD±0.228). In vivo imaging demonstrated clear contrast of the orthotopic tumors with minimal background signal. No toxicity was observed.

Conclusion: MUC5AC-IR800 provides distinct visualization of liver metastasis of pancreatic cancer in a patient derived orthotopic xenograft mouse model. Given the successful imaging of liver metastasis of pancreatic cancer with MUC5AC-IR800, this compound has clinical potential to detect primary pancreatic tumors as well as metastatic deposits. This technology could be used in FGS and operative staging of

pancreatic cancer.



Patient derived metastatic pancreatic cancer orthotopically implanted in the liver of a nude mouse, yellow arrow (panel A) and targeted with MUC5AC-IR800 (panel B). The red scale represents 1 cm.

13. INTERPLAY BETWEEN CHECKPOINT MOLECULE B7-H3 AND HUMAN LEUCOCYTE ANTIGEN CLASS I EXPRESSION: RELEVANCE TO THE CLINICAL COURSE OF PANCREATIC DUCTAL ADENOCARCINOMA

T Michelakos, F Kontos, A Sadagopan, L Cai, V Villani, F Sabbatino, T Sherwood, F Chen, PA. Moore, S Ferrone, CR Ferrone

Presenter: Theodoros Michelakos MD | Massachusetts General Hospital, United States

Background: Human leucocyte antigen (HLA) class I expression defects may provide malignant cells with an immune escape mechanism and have been associated with poor prognosis in various cancers. However, this association is not universal across studies. Whether this discrepancy reflects the modulation by the checkpoint molecule B7-H3 of the role of HLA class I in pancreatic ductal adenocarcinoma (PDAC) is unknown.

Methods: Resected PDACs (1998-2011) were immunohistochemically analyzed for HLA-A, HLA-B/C and B7-H3 expression, and immune cell infiltration. Gene correlation was analyzed using public databases.

Results: Of the 130 PDACs, HLA-A and HLA-B/C expression was defective in 75% and 59%, respectively. HLA class I and B7-H3 expression were positively correlated at the protein (p=0.006) and mRNA (p<0.001) levels, possibly because of the shared transcriptional regulator RFX5. High B7-H3 expression (HR=2.1;p=0.011) and low CD8+ cell density (HR=2.1;p=0.008) were predictors of poor overall survival (OS), but HLA class I was not, despite its known role in cancer cell elimination by cognate T-cells. Therefore, we investigated whether its role was influenced by B7-H3, which inhibits cytotoxic T-cells. Indeed, defective HLA-A (p=0.027) and HLA-B/C (p=0.004) expression correlated with poor OS only among patients with low B7-H3 expression (Figure). Conversely, low B7-H3 expression was associated with longer OS only when HLA class I expression was high (p=0.001).

Conclusion: Our findings may explain the inconsistent association between HLA class I expression and malignant disease prognosis. The negative impact of B7-H3 on PDAC prognosis emphasizes the need to develop B7-H3-blocking antibodies. These molecules may be clinically relevant provided tumors express high levels of HLA class I.

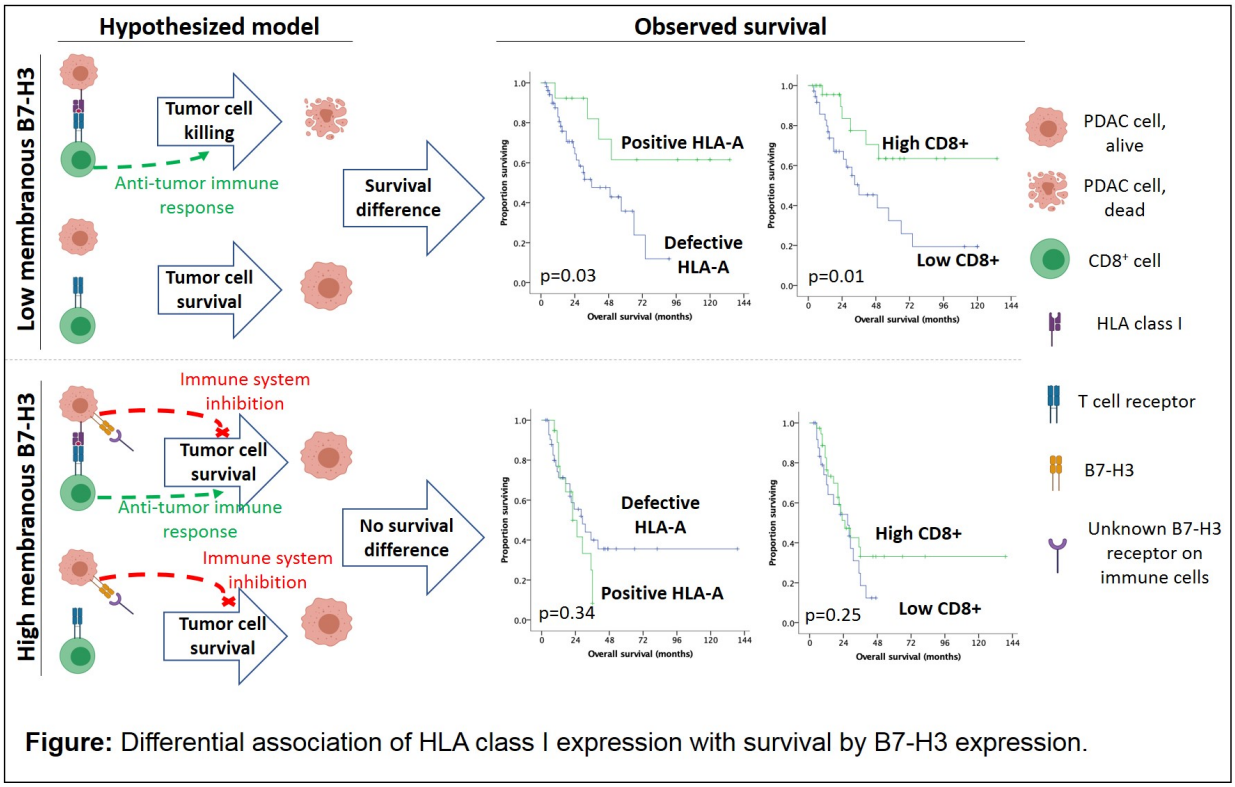


Figure: Differential association of HLA class I expression with survival by B7-H3 expression.

14. TARGETING DNA REPAIR PROTEIN, BARD1, IN PANCREATIC DUCTAL ADENOCARCINOMA

A Jain, JR Brody, CJ Yeo
Presenter: Aditi Jain PhD | Thomas Jefferson University, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death in the U.S., and is on course to become the second leading cause by 2030. PARP inhibitors (PARPi)/platinum therapies have demonstrated clinical efficacy in BRCA1/2 mutated PDAC and has recently led to the FDA approval of olaparib (Lynparza) in the maintenance setting. Although promising for a subset of PDAC patients, there is still a huge unmet need for better targets and targeted therapies. BRCA-Associated-Ring-Domain-1 (BARD1) is the main binding partner of BRCA1 and formation of BRCA1/BARD1 complex is essential for DNA repair in the cells. BARD1 mRNA is significantly overexpressed in PanINs and PDAC tissues. Our initial findings suggest that BARD1 gene expression is upregulated by an RNA binding post-transcriptional mechanism in cells exposed to DNA damage agents. Therefore, we hypothesize that BARD1 plays an oncogenic role in PDAC and its inhibition sensitizes cells to DNA damage agents. In this study, we evaluated how targeting BARD1 in PDAC cells effects drug sensitivity to DNA damage agents and whether BARD1 regulates acquired PARP inhibitor/platinum drug resistance.

Methods: PDAC cell lines (MiaPaCa-2/Panc-1) were transiently transfected by BARD1 specific siRNA and drug sensitivity was analyzed by Pico Green cell survival assays and colony formation assays. DNA-damage was assessed by comet assays and γ-H2AX staining. DNA repair efficiency was evaluated by HR-DRGFP reporter assay. Propidium iodide (PI) DNA staining assessed changes in cell cycle. RNA-seq analysis and RT-qPCR analyzed BARD1 dependent effects on cell cycle genes. PARPi resistant cell lines were created by chronic treatment of cells with IC50 dose of olaparib for over two months.

Results: Transient transfection of BARD1 siRNA in PDAC cell lines inhibited cell growth and enhanced sensitivity of PDAC cells to two components of standard of care therapy (FOLFIRINOX), oxaliplatin (Eloxatin) and irinotecan (Camptosar), as well as olaparib, as analyzed by Pico Green and colony formation assays. Using flow cytometery and PI staining cell cycle analysis, we found that inhibition of BARD1 causes G2-M cell cycle arrest. This was accompanied by an increase in DNA-damage and a decrease in DNA repair efficiency. We found a significant ($p<0.005$) downregulation of cell cycle genes and DNA repair pathways from RNA-sequence analysis of BARD1 siRNA cells, compared to control cells (siCONTROL). We created acquired PARPi (olaparib) resistant cell lines that are cross resistant to oxaliplatin and found that protein expression of BARD1 is upregulated in resistant cell lines, targeting of which sensitizes these cells to PARPi therapy.

Conclusion: In conclusion, PDAC are in general, genetically unstable and highly reliant on DNA repair proteins for survival and evasion from chemotherapeutic exposure. In this study, we found that targeting BARD1 provides an exciting therapeutic opportunity with the potential to greatly benefit PDAC patient outcomes. Future studies are aimed to explore the effects of targeting BARD1 in a relevant mouse model of PDAC. We will also explore downstream signaling pathways regulated by BARD1 in PDAC in order to identify new therapeutic interventions and drug combinations.

15. NUCLEAR-TO-CYTOPLASM EXPRESSION OF HNF4ALPHA IN IPMN CARCINOGENESIS

J Wong, VQ Trinh, F Revetta, JT Roland, K DelGiorno, C Shi, MC Tan
Presenter: Jahg Wong MD | Vanderbilt University Medical Center, United States

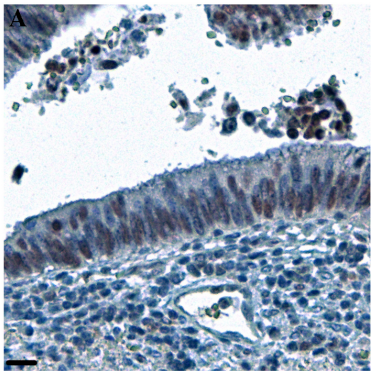
Background: The mechanisms of malignant transformation in intraductal papillary mucinous neoplasms (IPMN) are poorly understood. HNF4alpha is a transcription factor found in the liver, where loss of its nuclear expression is associated with hepatocyte dedifferentiation, epithelial-to-mesenchymal transformation and cancer progression. However, its role in pancreatic tumorigenesis has not been studied.

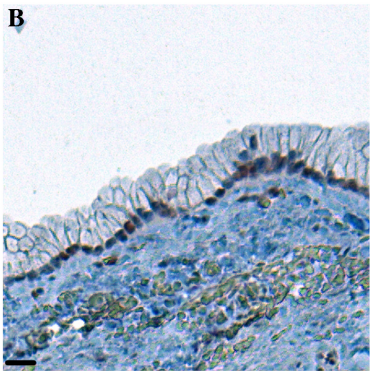
Methods: Immunohistochemical studies of HNF4alpha were performed on 53 resected IPMN and 4 normal pancreas controls. IPMN were categorized by histologic type (gastric-foveolar, intestinal, pancreaticobiliary), and dysplasia (low-grade, high-grade, invasive). Two independent observers scored density and subcellular localization (nuclear vs cytoplasmic) of HNF4alpha expression.

Results: In IPMN, HNF4alpha expression was increased in high-grade and invasive components compared to low-grade components (Kruskal-Wallis $p = 0.0230$). Strong diffuse expression did not vary by histologic type (gastric-foveolar 15/21, intestinal 10/16, pancreaticobiliar 10/16; $p = 0.801$). Low-grade IPMNs showed strict nuclear expression, while in high-grade dysplasia there was a shift to cytoplasmic-predominant expression (low-grade 3/28; high-grade 8/15, $p = 0.002$). In invasive IPMN, areas of poorly differentiated histology (with sarcomatous features) were more likely (8/9) to have cytoplasmic HNF4alpha expression than areas of well-differentiated histology (tubulo-papillary, 0/6). All areas of tumor budding (11/11) showed strong cytoplasmic expression and reduced nuclear staining.

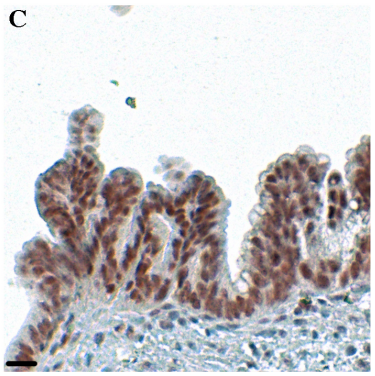
Conclusion: Two changes in HNF4alpha expression was associated with IPMN carcinogenesis: increased overall expression of HNF4alpha and, more importantly, a shift from nuclear to cytoplasmic expression. This nuclear HNF4alpha loss mirrors findings in hepatic carcinogenesis. Further functional studies to confirm the role of HNF4alpha-driven metabolic changes in IPMN are ongoing.

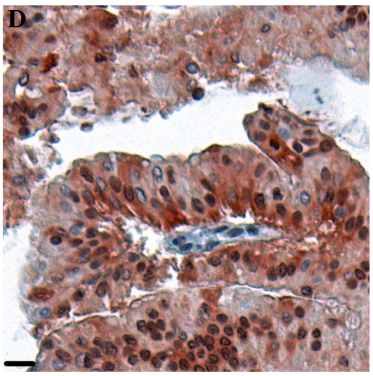
Low-grade IPMN epithelium



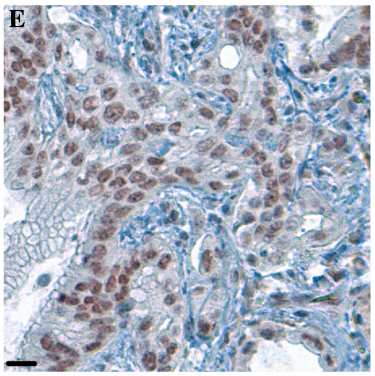


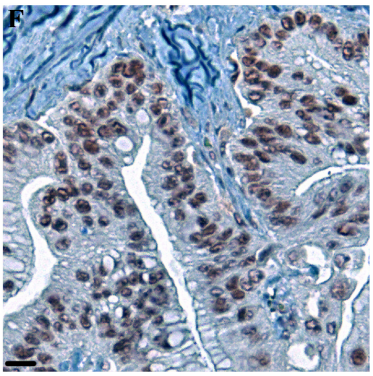
High-grade IPMN epithelium



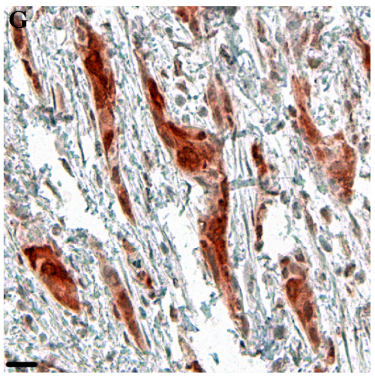


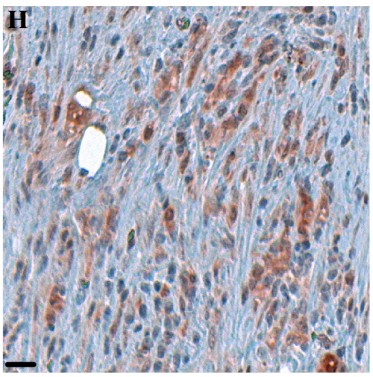
Tubulopapillary invasive component





Sarcomatoid invasive component





16. IMPACT OF THE 'CLASSICAL' AND 'BASAL-LIKE' MOLECULAR SUBTYPES OF PANCREATIC CANCER ON OVERALL SURVIVAL (SPACIOUS-2): A MULTICENTER STUDY

JA Suurmeijer, EC Soer, MP Dings, Y Kim, M Strijker, BA Bonsing, L Brosens, OR Busch, L Deguerre, J Groen, H van Laarhoven, IQ Molenaar, H Morreau, MJ van de Vijver, JW Wilmink, A Farina, J Verheij, MG Besselink, MF Bijlsma, F Dijk

Presenter: Annelie Suurmeijer MD | Academic Medical Center, Netherlands

Background: Molecular subtyping of pancreatic cancer is expected to improve the design of clinical trials aiming for a more tailored approach to neoadjuvant and adjuvant treatment. It is currently unclear whether the subtypes of pancreatic cancer are independent predictors of overall survival (OS) when taking both clinical and histopathological (i.e. after resection) parameters into account. This field is moving towards a two-tier classification scheme with a 'classical' and a more aggressive 'basal-like' pancreatic cancer subtype. However, implementation in clinical practice remains challenging due to costs and the amount of tissue needed to determine the subtype. The recently published Purity Independent Subtyping of Tumors (PurIST) method is a robust classifier that could potentially be used on small biopsies, enabling its clinical implementation in the preoperative setting where complete histopathological assessment is lacking. In this study, we examined the prognostic value of PurIST in an extensively characterized multicenter cohort of patients with pancreatic cancer and provide tools for its clinical implementation.

Methods: Fresh frozen resection specimens used for RNA sequencing were retrospectively collected from three Dutch university hospitals. We performed PurIST classification on a cohort of 199 patients after pancreatic resection with curative intent for pancreatic cancer. Relevant patient, tumor, and treatment characteristics were compared between two subtypes (classical and basal-like). Univariable logistic regression analysis was used to test the association with basal-like subtype. Kaplan-Meier survival analysis and Cox proportional hazards regression analysis with backward selection were used to assess the prognostic value of subtyping in both the pre-operative and post-operative setting.

Results: Overall, 160 patients (80.4%) had a classical and 39 patients (19.6%) had a basal-like subtype of pancreatic cancer. Male sex (OR = 0.48, 95%CI = 0.22-0.98, p = 0.047), poor differentiation grade (OR = 2.39, 95%CI = 1.13-5.37, p = 0.03) and perineural growth (OR = 3.55, 95%CI = 1.18-15.35, p = 0.045) were associated with basal-like subtype. Patients with a classical subtype showed better OS than patients with a basal-like subtype (16 vs 9 months, HR 1.70, 95% CI = 1.18-2.44, P = 0.004). In multivariate cox regression analysis including only clinical parameters, the basal-like subtype was a predictor for poor OS (HR = 1.73, 95%CI = 1.20-2.50, P = 0.003). In multivariable cox regression analysis including all relevant clinical as well as histopathological parameters, the basal-like subtype remained a predictor for poor OS (HR = 1.50, 95%CI = 1.01-2.32, P = 0.044).

Conclusion: The basal-like subtype predicts poor survival (OS) in pancreatic cancer, also when taking postoperative histopathological parameters into account. Therefore, subtyping such as with the PurIST classifier can be helpful in the design of future randomized trials to help stratify and guide treatment decisions.

17. POSTPONED OR IMMEDIATE DRAINAGE OF INFECTED NECROTIZING PANCREATITIS (POINTER): A MULTICENTER RANDOMIZED TRIAL

L Boxhoorn L, SM van Dijk, J van Grinsven, RC Verdonk, MA Boermeester, TL Bollen, SAW Bouwense, MJ Bruno, VC Cappendijk, CHC Dejong, P van Duijvendijk, CHJ van Eijck, P Fockens, MFG Francken, H van Goor, M Hadithi, NDL Hallensleben, JW Haveman, MAJM Jacob

Presenter: Marc G. Besselink MD | Academic Medical Center, Netherlands

Background: Infected necrotizing pancreatitis is a potentially lethal disease treated by a step-up approach, with catheter drainage as first step. Patient outcome may be improved by early catheter drainage, but supporting evidence is limited.

Methods: We conducted a multicenter randomized trial in 22 Dutch hospitals, to determine whether immediate catheter drainage is superior to postponed catheter drainage in patients with infected necrotizing pancreatitis. Immediate catheter drainage included treatment with antibiotics and catheter drainage within 24 hours after patients were diagnosed with infected necrosis. Postponed catheter drainage included treatment with antibiotics and supportive treatment, aimed to postpone the drainage procedure until necrosis became walled-off. The primary end point was the Comprehensive Complication Index (CCI), combining all complications during 6 months of follow-up.

Results: In total, 104 patients were randomly assigned to immediate catheter drainage (55 patients) or postponed catheter drainage (49 patients). The median CCI was 56.46 (IQR 34.46-80.47) in the immediate drainage group and 48.22 (IQR 39.05-83.29) in the postponed drainage group (P=0.97). No significant difference between the immediate and postponed drainage group was observed in the rate of new-onset organ failure (25% and 22%; RR 1.13, 95%CI 0.57-2.26, P=0.82) and death (13% and 10%; RR 1.25, 95%CI 0.42-3.68, P=0.77). The median number of interventions for infected necrosis was 4 (IQR 2-6) and 1 (IQR 0-5) (P < 0.001). The length of intensive care stay was equal in both groups (median 0 days [IQR 0-8] vs. 0 days [IQR 0-8], P=0.76) and total hospital did not differ significantly (median 48 days [36-83] vs. 35 days [21-66], P=0.07). In the postponed drainage group, 19 patients (39%) were successfully treated with antibiotics alone, with 17 surviving patients at the end of 6 months follow-up.

Conclusion: Immediate catheter drainage in patients with infected necrotizing pancreatitis is not superior to postponed catheter drainage in reducing CCI. With a postponed catheter drainage strategy including antibiotic treatment, less interventions or infected necrosis are needed and more than one-third of patients may be treated conservatively.

18. CONTEMPORARY INTERVENTION IN NECROTIZING PANCREATITIS: IMPROVED UNDERSTANDING CHANGING PRACTICE

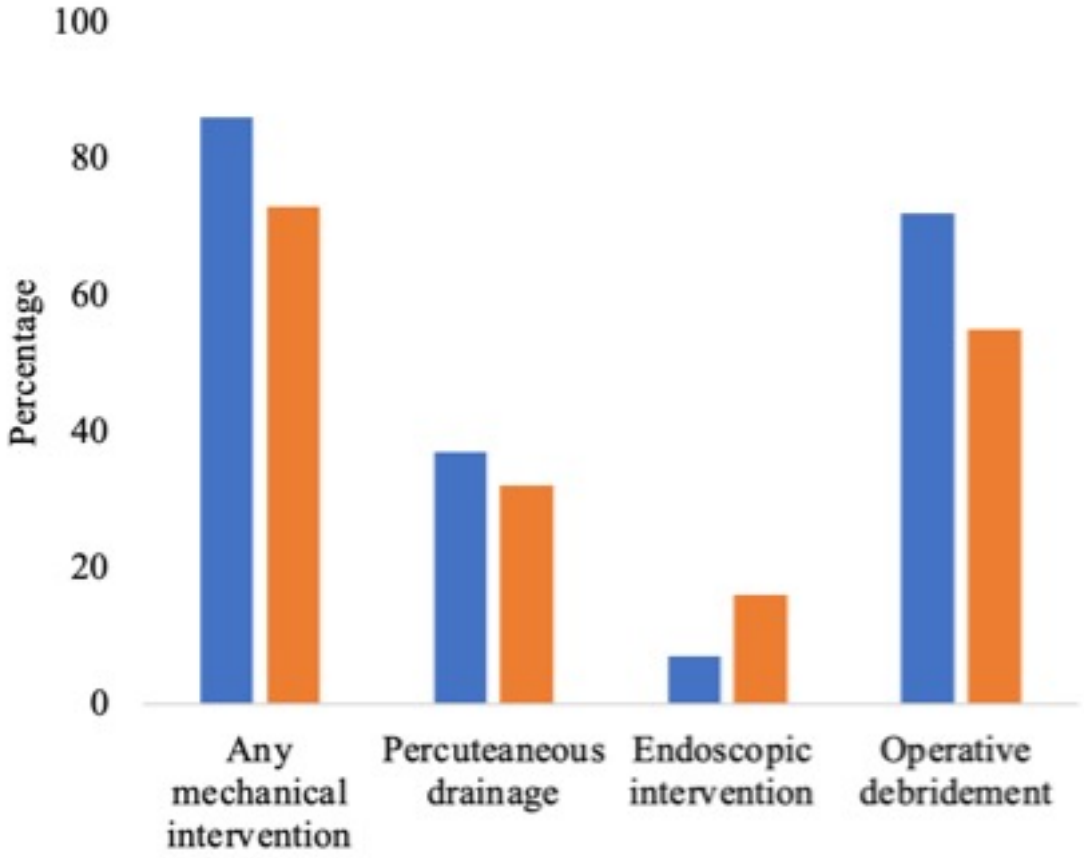
SP McGuire, TK Maatman, EP Ceppa, MG House, A Nakeeb, TK Nguyen, CM Schmidt, NJ Zyromski
Presenter: Sean McGuire MD | Indiana University School of Medicine, United States

Background: Treatment of necrotizing pancreatitis (NP) has shifted in favor of a minimally invasive step-up approach rather than early open pancreatic debridement. We hypothesized that this paradigm shift would be reflected in the intervention, morbidity, and mortality profile of NP patients.

Methods: Single institution retrospective review of 770 NP patients treated between 2005-2019. Two eras of NP intervention were identified relative to the introduction of a minimally invasive approach to NP. Patients treated from 2005-2010 were classified as the "early" group and compared with patients treated from 2011-2019, classified as the "late" group.

Results: 299 NP patients comprised the early group and 468 patients comprised the late group. No differences were seen in patient demographics, comorbidity profile, or NP etiology between groups. Percent necrosis, necrosis location, CT severity index (CTSI), and rates of infected necrosis were unchanged between groups. No difference was seen in mortality. Mechanical intervention for NP was more common in the early than the late group (86% vs. 73%, p<0.001). Time to first intervention was similar between groups (79 □ 7d vs. 75 □ 6d). The early group had higher rates of open pancreatic debridement (72% vs. 55%, p<0.001). Endoscopic intervention was less common in the early than the late group (7% vs. 16%, p<0.001). NP disease duration was longer in the early than the late group (223 □ 12d vs. 179 □ 7d, p = 0.001).

Conclusion: Contemporary management of necrotizing pancreatitis is marked by less frequent operative debridement and shorter disease duration.



19. OPTIMAL TIMING OF CHOLECYSTECTOMY AFTER NECROTISING BILIARY PANCREATITIS

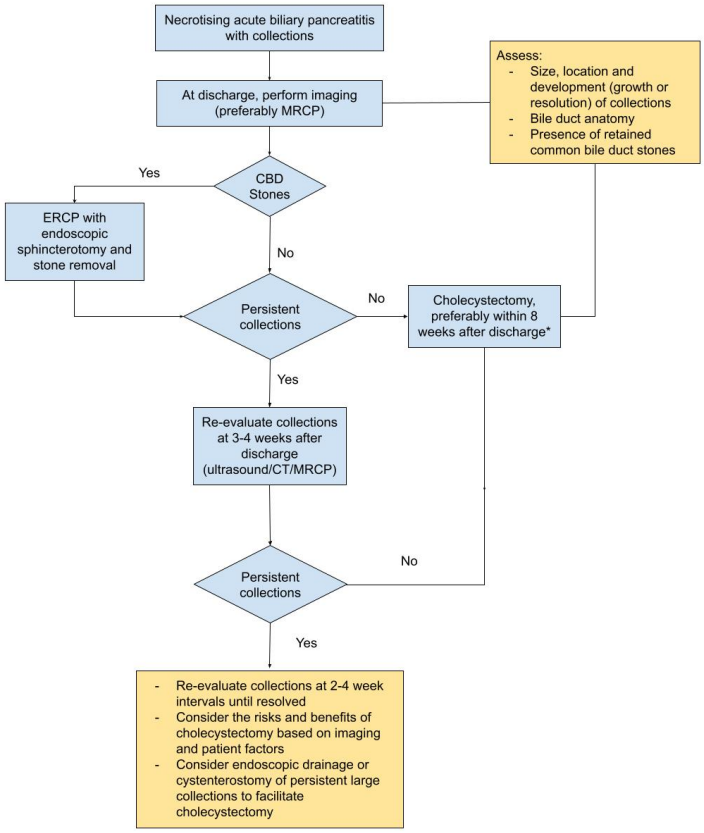
H Timmerhuis, N Hallensleben, R Hollemans, S Pocornie, J van Grinsven, S van Brunschot, O Bakker, R van der Sluijs, M Schwartz, P van Duijvendijk, T Romkens, M Besselink, T Bollen, S Bouwense, H van Santvoort, M Bruno
Presenter: Hester Timmerhuis MD | St. Antonius Hospital, Netherlands

Background: Following an episode of acute biliary pancreatitis, cholecystectomy is advised to prevent recurrent biliary events. There is limited evidence regarding the optimal timing and safety of cholecystectomy in patients with necrotising biliary pancreatitis.

Methods: A post-hoc analysis of a multicentre prospective cohort. Patients with biliary pancreatitis and a computed tomography severity score of three or more were included in 27 Dutch hospitals between 2005 and 2014. Primary outcome was the optimal timing of cholecystectomy in patients with necrotising biliary pancreatitis. Secondary outcomes were the number of recurrent biliary events, periprocedural complications of cholecystectomy, and the protective value of endoscopic sphincterotomy.

Results: Overall, 248 patients were included in the analysis. Cholecystectomy was performed in 191 patients (77%) at a median of 103 days (IQR 46 – 222) after discharge. Infected necrosis after cholecystectomy occurred in four (2%) patients with persistent peripancreatic collections. Before cholecystectomy, 66 patients (27%) developed biliary events. The risk of overall recurrent biliary events prior to cholecystectomy increased significantly at 10 weeks after discharge (risk ratio 0.493 [95% CI 0.270 – 0.900]; p = 0.016). The risk of recurrent pancreatitis before cholecystectomy increased significantly at 8 weeks after discharge (risk ratio 0.135 [0.018 – 0.987]; p = 0.018). The complication rate of cholecystectomy did not = decrease over time. Endoscopic sphincterotomy did not reduce the risk of recurrent biliary events (odds ratio 1.4 [95% CI, 0.74–2.83]).

Conclusion: The optimal timing of cholecystectomy after necrotising biliary pancreatitis, in the absence of peripancreatic collections, is within 8 weeks after discharge. There is no role for endoscopic sphincterotomy to prevent recurrent biliary events in patients with necrotising biliary pancreatitis.


Necrotising acute biliary pancreatitis with collections
At discharge, perform imaging (preferably MRCP)
Assess:
- Size, location and development (growth or resolution) of collections
- Bile duct anatomy
- Presence of retained common bile duct stones
CBD Stones
Yes
ERCP with endoscopic sphincterotomy and stone removal
No
Persistent collections
No
Cholecystectomy, preferably within 8 weeks after discharge*
Yes
Re-evaluate collections at 3-4 weeks after discharge (ultrasound/CT/MRCP)
Persistent collections
No
Yes
- Re-evaluate collections at 2-4 week intervals until resolved
- Consider the risks and benefits of cholecystectomy based on imaging and patient factors
- Consider endoscopic drainage or cystenterostomy of persistent large collections to facilitate cholecystectomy

20. SPLANCHNIC VENOUS THROMBOSIS IN NECROTIZING PANCREATITIS: COMMON, HETEROGENOUS, AND DEADLY

SP McGuire, TK Maatman, EP Ceppa, JJ Easler, E Fogel, MG House, A Nakeeb, TK Nguyen, CM Schmidt, NJ Zyromski

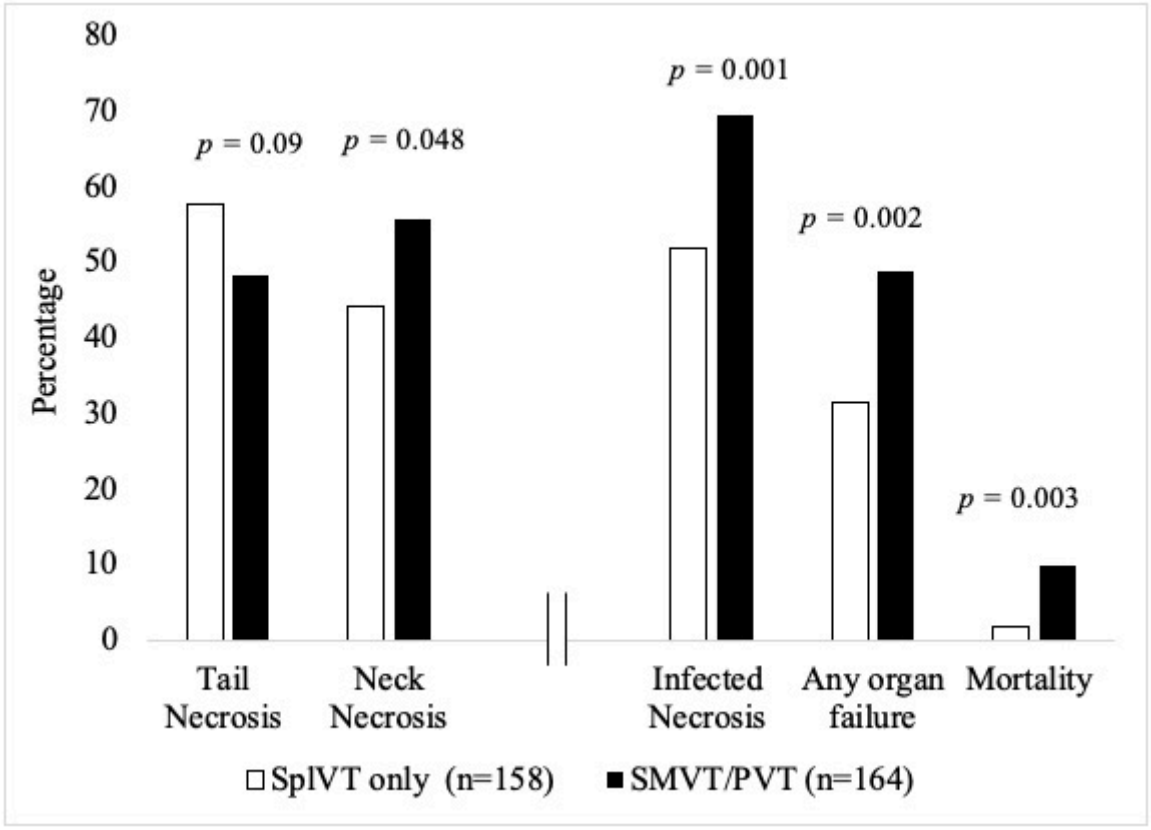
Presenter: Sean McGuire MD | Indiana University School of Medicine, United States

Background: The inflammatory insult of necrotizing pancreatitis (NP) increases rates of venous thromboembolism, including splanchnic venous thrombosis (SVT). The natural history of SVT in NP is incompletely understood. We hypothesized that NP patients with SVT would have more severe pancreatic necrosis and higher rates of NP-associated morbidity.

Methods: Single institution retrospective review of 745 NP patients treated between 2005-2019. We compared the comorbidity profile, necrotizing pancreatitis severity and disease course, and short-term outcomes between patients with and without SVT. Statistical significance was determined using t-test, chi-square, or ANOVA; P-values less than 0.05 were accepted as significant.

Results: The overall incidence of SVT was 43% (322/745 NP patients). Isolated splenic venous thrombosis (SplVT) was the most common anatomic distribution (49%), followed by combined superior mesenteric venous thrombosis (SMVT) and SplVT (14%), isolated portal vein thrombosis (PVT) (10%), combined PVT, SMVT, and SplVT (9%), combined PVT and SplVT (7%), isolated SMVT (6%), and combined PVT and SMVT (5%). SVT was diagnosed an average of 97 □ 14 days after NP diagnosis. Patients with SVT were more likely to be male (71% versus 60%, p = 0.002). No differences in pre-existing comorbidities or NP etiology were seen between patients with and without SVT. Patients with SVT had more severe pancreatic necrosis: the average CTSI in patients with SVT was 7.1 □ 0.4 compared to 6.3 □ 0.1 in patients without SVT (p50% necrosis compared to 19% of patients without SVT (p<0.001). Patients with SVT were more likely to have infected necrosis (61% vs 48%, p<0.001). Disease duration was longer in patients with SVT (228 □ 12.6 days) compared to patients without SVT (171 □ 6.2 days) (p <0.001). The location of pancreatic necrosis correlated with the location of venous thrombosis (Figure). Significant heterogeneity in disease course and outcomes was observed relative to the location of venous thrombus. Patients with PVT, SMVT, or multi-vein involvement had significantly greater rates of infected necrosis, organ failure, and mortality than those with isolated SplVT (Figure).

Conclusion: Splanchnic venous thrombosis is very common in necrotizing pancreatitis. More severe necrosis is associated with an increased likelihood of SVT development. SVT is associated with prolonged disease course; however, NP disease course and mortality rates vary depending on venous thrombus location, suggesting that SVT is a heterogenous problem requiring an individualized approach to management.


80
70
60
50
40
30
20
10
0
Percentage
p = 0.09
p = 0.048
p = 0.001
p = 0.002
p = 0.003
Tail Necrosis
Neck Necrosis
Infected Necrosis
Any organ failure
Mortality
SplVT only (n=158)
SMVT/PVT (n=164)

21. CHANGING STRATEGIES IN THE MANAGEMENT OF CHRONIC PANCREATITIS SINCE THE INTRODUCTION OF TOTAL PANCREATECTOMY WITH ISLET AUTO-TRANSPLANTATION (TPIAT)

R Srivastava, S Owczarski, M Walters, H Wang, D Adams, W Lancaster, K Morgan
Presenter: Romik Srivastava MD | Academic Medical Center, United States

Background: Selected patients with chronic pancreatitis (CP) intractable to medical and endoscopic management may be candidates for surgical management with total pancreatectomy with islet auto-transplantation (TPIAT). How has the introduction of TPIAT influenced the utilization of traditional drainage and resection procedures in the management of chronic pancreatitis?

Methods: A retrospective review and analysis of patients managed at a single center was undertaken to compare operative selection in a cohort of patients managed prior to the introduction of TPIAT with those managed thereafter. Pancreatic operations of 372 patients managed from 1995-2003 and previously reported in a retrospective review (J Am Coll Surg. 2007;204:1039-45) were compared with a cohort of 434 patients managed with conventional resection and drainage procedures (217 patients) and TPIAT (217 patients) from 2010-2018 identified in an IRB approved prospective data base. Selections of operative procedures and CP risk factors over two historical 8-year periods were compared.

Results: In the pre-TPIAT cohort of 372 patients 26% underwent pancreaticoduodenectomy (PD or Whipple), 49% had a longitudinal pancreaticojejunostomy (LPJ), 25% had a distal pancreatectomy (DP). The three most common risk factors for CP were alcohol abuse (46%), idiopathic (16%), and gallstones (16%). In the post-TPIAT cohort, the operative distribution was: 13% PD, 13% LPJ, 26% DP, and 50% TPIAT. The three most common risk factors for CP in the post TPIAT group who had conventional surgery were alcohol abuse (40%), idiopathic (21%), and gallstones (14%). The most common risk factors in the TPIAT cohort were hereditary pancreatitis (28%), papillary stenosis (25%), and idiopathic (20%).

Conclusion: Available strategies in the operative management of chronic pancreatitis have changed since the introduction of TPIAT. There has been a significant decrease in selection of PD's/Whipple's and LPJ's with an increase in DP's. These changes are reflected in an increasing number of patients identified with hereditary chronic pancreatitis with an increasing number of patients being managed with TPIAT.

22. SUPERIOR MESENTERIC ARTERY RESECTION DURING PANCREATECTOMY: POST-OPERATIVE RESULTS AND SURVIVAL

N Napoli, EF Kauffmann, M Ginesini, C Gianfaldoni, F Asta, C Cappelli, D Campani, F Vistoli, U Boggi
Presenter: Niccolò Napoli MD | University of Pisa, Italy

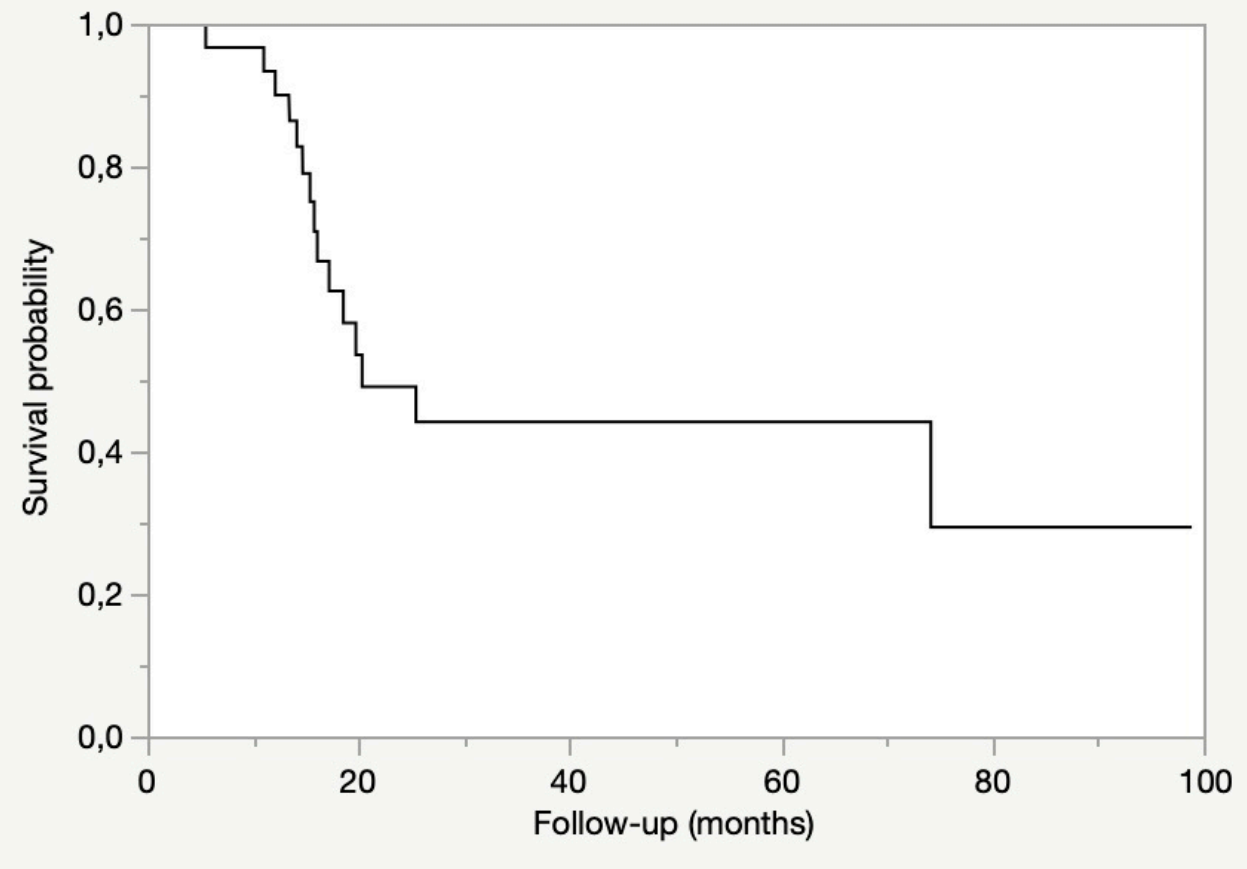
Background: We herein reported our experience about en-bloc resection of superior mesenteric artery (SMA) during pancreatectomy (SMA-P).

Methods: We performed a retrospective study of patients who underwent SMA-P between 1994 and 2021. The pathological findings are exclusively reported for pancreatic ductal adenocarcinoma (PDAC). Kaplan-Meier curve was used to evaluate long-term survival and univariate cox proportional hazard regression to identify prognostic factors. Only pancreatic ductal adenocarcinoma (PDAC) with a minimum follow-up of 2 years were considered for survival analysis.

Results: Sixty-eight patients (52.9% male, mean□SD of 61□9.2 years, median ASA score of 2) underwent SMA-P (61 total pancreatectomy and 7 pancreaticoduodenectomy). The number of SMA resections and the proportion of patients receiving neoadjuvant therapies increased progressively over the study period. The celiac trunk/hepatic artery and the portal vein/superior mesenteric vein were resected concurrently to SMA in 22 (32.4%) and 65 (95.6%) patients, respectively. The SMA was reconstructed by direct anastomosis in 36 patients (52.9%). A jump graft, either autologous or cadaveric, was used in 12 (17.6 %) patients and a switched splenic artery in 20 (29.4 %) patients. Median length of stay was 22 (15.3-30) days. Severe POC occurred in 15 (22.1%) patients (C-D IIIB: 4 [5.9%]; C-D IVA: 1 [1.5%]; C-D IVB: 1 [1.5%]; C-D V: 9 [13.2%]). Ductal adenocarcinoma was the final diagnosis in 51 (75%) patients. An R0 resection was obtained in 39 patients (76.5 %). Lymph nodes (LN) metastasis were present in 45 (88.2%) (N1= 24 [35.3%], N2= 19 [41.2%]) patients with a median LN ratio of 4 (2.5-8.2) and a mean LODDS of -2.9±1.1. The latter figure was inferior in patients underwent neoadjuvant therapy (-3.±0.2) rather than upfront surgery (-2.2±0.3) (p=0.04). Median disease specific survival (DSS) was 20.2 (15.7-NA) months (fig. 1). There were three patients who survived longer than 5 years. The median LN ratio (HR= 1.14; p=0.02) and the mean LODDS (HR= 2.72; p=0.006) affected both the median DSS.

Conclusion: En-bloc resection of SMA during pancreatectomy is a formidable operation and long-term survival remains a rare and largely unpredictable event, but these results encourage to further

investigation.



23. AMPULLARY NEUROENDOCRINE TUMORS: A WINDOW INTO A RARE TUMOR

S Ruff, O Standring, G Wu, A Levy, S Anantha, E Newman, M Karpeh Jr., W Nealon, G Deutsch, M Weiss, D DePeralta

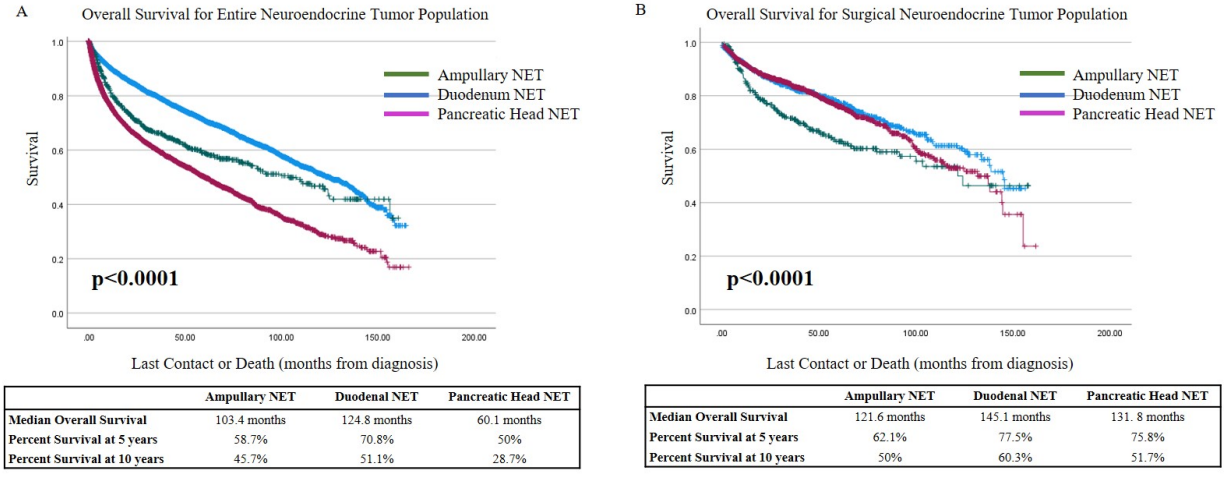
Presenter: Samantha Ruff MD | Northwell Health, United States

Background: Ampullary neuroendocrine tumors (NETs) make up <1% of all gastrointestinal NETs and information about their behavior and prognosis relies on case series. This study describes the population of patients diagnosed with ampullary NETs and compares them to patients with duodenal and pancreatic head NETs.

Methods: The National Cancer Database (2004 – 2016) was queried for patients with ampullary, duodenal and pancreatic head NETs. Clinicopathologic and treatment characteristics were compared. Kaplan Meier analysis and Cox regression were used to analyze survival.

Results: Overall, 872, 9692, and 6561 patients were identified with ampullary, duodenal, and pancreatic head NETs, respectively. Patients with ampullary NETs had more grade 3 tumors (N&#3f149, 17%) than patients with duodenal (N&#3f197, 2%) or pancreatic head (N&#3f740, 11%) NETs. Patients with ampullary NETs had more positive lymph nodes (N&#3f297, 34%) than patients with duodenal (N&#3f950, 10%) or pancreatic head (N&#3f1513, 23%) NETs. On multivariable analysis for patients with ampullary NETs, age (HR 1.03, p<0.0001), Charlson-Deyo (CD) score of 2 (HR 2.3, p=0.001) or ≥3 (HR 2.9, p=0.013), grade 2 (HR 1.9, p=0.007) or grade 3 tumors (HR 4.0, p<0.0001), and metastatic disease (HR 2.0, p=0.001) were associated with increased mortality. At five years, the overall survival for patients with ampullary, duodenal, and pancreatic head NETs was 59%, 71%, and 50%, respectively (p<0.0001). In the ampullary NET surgical population (N&#3f366), multivariable analysis showed that age (HR 1.04, p=0.002), CD score of 2 (OR 5.8, p<0.0001) or ≥3 (OR 17.4, p=0.026), and grade 3 tumors (HR 4.6, p<0.0001) were associated with increased mortality. The five-year survival for patients with ampullary, duodenal, and pancreatic head NETs who underwent surgery was 62%, 78%, and 76% respectively (p<0.0001).

Conclusion: This study sheds light on a rare tumor histology. Compared to patients who underwent surgical resection for duodenal or pancreatic head NETs, patients with ampullary NETs had a significantly worse prognosis. This, combined with the difference in tumor grade and lymph node status at diagnosis, suggests that ampullary NETs have a unique biology compared to duodenal and pancreatic head NETs. Identifying prognostic factors allows us to create more concrete guidelines and provide patients with improved prognostic information.



	Ampullary NET	Duodenal NET	Pancreatic Head NET
Median Overall Survival	103.4 months	124.8 months	60.1 months
Percent Survival at 5 years	58.7%	70.8%	50%
Percent Survival at 10 years	45.7%	51.1%	28.7%

	Ampullary NET	Duodenal NET	Pancreatic Head NET
Median Overall Survival	121.6 months	145.1 months	131. 8 months
Percent Survival at 5 years	62.1%	77.5%	75.8%
Percent Survival at 10 years	50%	60.3%	51.7%

Kaplan Meier analysis comparing overall survival of ampullary, duodenal, and pancreatic head neuroendocrine tumors for A) the entire population and B) the surgical population

24. ARTERIAL DIVESTMENT OR ARTERIAL RESECTION FOR LOCALLY ADVANCED PANCREAS CANCER

O Yoshino, M Aldakkak, B Seadler, S Tsai, RY Kim, M Kamgar, WA Hall, CN Clarke, B George, B Erickson, AH Khan, DB Evans, KK Christians

Presenter: Osamu Yoshino MD | Medical College of Wisconsin, United States

Background: The removal of part, or all, of the autonomic nerve which surrounds the SMA, hepatic and celiac arteries is a critically important part of pancreatectomy for cancer. This technique has recently been termed arterial divestment (AD) and is proposed as an alternative to arterial resection/reconstruction (AR) in some patients. In contrast, we have always emphasized the importance of developing the plane of dissection between the adventitia of the artery and the surrounding perineural tissue; if this plane is successfully developed, the artery is preserved -if this plane of dissection cannot be developed (tumor inseparable from adventitia) then the artery is resected and reconstructed. The aim of this study was to determine short- and long-term outcomes in patients with LAPC who underwent pancreatectomy with AD or AR.

Methods: We analyzed all patients with LAPC who underwent neoadjuvant therapy followed by pancreatectomy and required AD or AR, between January 2009 and July 2020. Patient demographics, clinical stage and perioperative data including complications and survival were reviewed. Median overall survival (mOS) was calculated from the date of diagnosis to the date of death or last follow-up.

Results: In total, 92 patients with LAPC underwent resection; AD in 70 (76%) patients and AR in 22 (24%). There was no difference between the two groups in key-demographics and pathological variables (Table 1). The 22 patients in the AR group required resection of a combination of any of the following arteries: celiac, common hepatic, proper hepatic, right hepatic, or left gastric artery. Of the 22 patients who required AR, 17 (77%) underwent revascularization with either primary anastomosis (n=7) or a saphenous vein graft (n=10). Simultaneous venous resection or mesocaval bypass were performed in 36 (51%) of the 70 patients in the AD group and in 1 (5%) of the 22 who underwent AR ($p<0.001$). There were no statistically significant differences between groups in operative time, estimated blood loss or complications of Clavien grade 3 or greater; there were no 90-day mortalities. Disease recurrence was observed in 43 (62%) of the 70 patients in the AD group and in 11 (52%) of the 22 patients who required AR ($p=0.45$); no difference was observed in local or distant recurrence rates. The mOS was 38.5 months; 35 months in those treated with AD and 56 months among the 22 patients who required AR ($p=0.02$). In an adjusted Cox proportional hazards model, AD vs. AR was not associated with an increased risk of death (HR:0.59, 95% CI: 0.25 – 1.41, $p=0.24$) however addition of portal vein resection (hazard ratio: 2.38, CI: 1.05 – 5.40, $p=0.03$) was.

Conclusion: In patients with LAPC due to tumor extension to adjacent visceral arteries, AR is performed when the plane of dissection cannot be developed between arterial adventitia and surrounding perineural tissue leaving arterial resection and reconstruction as the only way to avoid a positive margin. This approach to the management of tumor extension to the visceral arteries during pancreatectomy assumes the ability to safely resect and reconstruct the celiac or hepatic arteries when necessary.

25. HIGH-RISK PANCREATIC ANASTOMOSIS VS. TOTAL PANCREATECTOMY AFTER PANCREATODUODENECTOMY: POSTOPERATIVE OUTCOMES AND QUALITY OF LIFE ANALYSIS

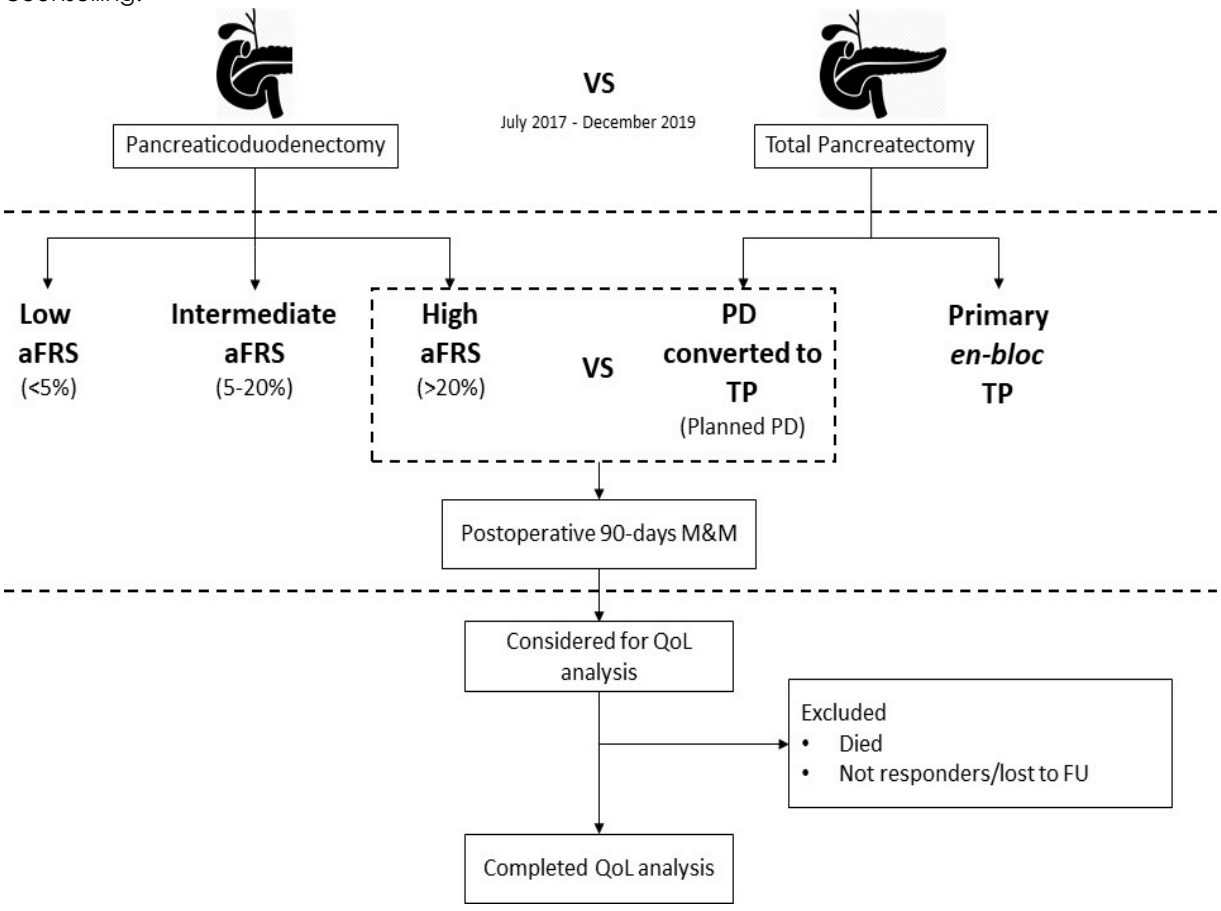
G Perri, G Marchegiani, A Burelli, F Zoccatelli, S Andrianello, C Bassi, R Salvia
Presenter: Giampaolo Perri MD | University of Verona, Italy

Background: This study evaluates total pancreatectomy (TP) as an alternative to pancreatoduodenectomy (PD) in patients at high-risk for postoperative pancreatic fistula (POPF). Outcomes of high-risk PD (HR-PD) and TP have never been compared before.

Methods: All patients who underwent PD or TP between July 2017 and December 2019 were identified. HR-PD was defined according to the alternative Fistula Risk Score. Postoperative outcomes (primary endpoint), pancreatic insufficiency and quality of life after 12 months of follow-up (QoL) were compared between HR-PD or planned PD intraoperatively converted to TP (C-TP).

Results: A total of 566 patients underwent PD and 136 underwent TP during the study period. One hundred one (18%) PD patients underwent HR-PD, while 86 (63%) TP patients underwent C-TP. Postoperatively, the patients in the C-TP group exhibited lower rates of post-pancreatectomy hemorrhage (15% vs 28%), delayed gastric emptying (16% vs 34%), sepsis (10% vs 31%), and Clavien-Dindo ≥3 morbidity (19% vs 31%) and had shorter median lengths of hospital stay (10 vs 21 days) (all $p < 0.05$). The rate of POPF in the HR-PD group was 39%. Mortality was comparable between the two groups (3% vs 4%). Although general, cancer- and pancreas-specific QoL were comparable between the HR-PD and C-TP groups, endocrine and exocrine insufficiency occurred in all the C-TP patients, compared to only 13% and 63% of the HR-PD patients respectively, and C-TP patients had worse diabetes-specific QoL.

Conclusion: C-TP may be considered rather than HR-PD only in few selected cases and after adequate counselling.



26. GRADING PANCREATIC NEUROENDOCRINE TUMORS ON ENDOSCOPIC ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION: A MULTI-INSTITUTIONAL STUDY

AA Javed, S Razi, A Pulvirenti, J Zheng, T Michelakos, Y Sekigami, AC Wei, AH Zureikat, CR Ferrone, J He
Presenter: Ammar Javed MD | Johns Hopkins University School of Medicine, United States

Background: World Health Organization (WHO) grading system is prognostic in pancreatic neuroendocrine tumors (PanNETs). The concordance between WHO grade on cytological analysis (c-grade) of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and histopathological analysis (h-grade) of surgical specimen is reported to be between 60 and 80%. Factors associated with concordance and trends of utilization of EUS-FNA for grading of PanNETs remain poorly understood.

Methods: A multicenter retrospective study was performed on patients undergoing resection for PanNETs at four high-volume centers. Patients with functional or syndrome associated tumors, and those who received neoadjuvant therapy were excluded. Factors associated with concordance between c-grade and h-grade and trends of utilization of EUS-FNA for PanNETs over the last two decades were assessed.

Results: Of the 1,329 patients included, 682 (51.1%) underwent EUS-FNA; 567 (83.1%) were diagnostic of PanNETs and WHO grade was reported for 293 (51.7%) patients. The concordance between c-grade and h-grade was 78.2% with moderate interrater agreement (Kc=0.48, p<0.001). Significantly higher rates of concordance were observed in patients with smaller tumors (< 2 vs. ≥2 cm, 88.9% vs. 72.7%, p=0.001). The highest concordance was 97.9%and was observed in patients with small tumors undergoing assessment between 2015-2019; near perfect interrater agreement (Kc=0.88, p<0.001)
Over the last two decades an increase in the utilization of EUS-FNA from 46.7% to 62.1% was observed (p<0.001). Furthermore, EUS-FNA was more frequently diagnostic of PanNETs (p<0.001), and WHO grade was more frequently reported (< 0.001). Despite increased utilization of EUS-FNA the rate of concordance did not change (p=0.056).

Conclusion: Recently, a trend towards increases utilization and improved diagnostic accuracy of EUS-FNA has been observed in PanNETs. Concordance between c-grade and h-grade is associated with tumor size. In the current era a near perfect agreement exists between c-grade and h-grade in small PanNETs.

27. A DIFFICULTY SCORE FOR ROBOTIC PANCREATICODUODENECTOMY: THE ROBOTIC ADDICT SCORE

C Cacace, N Napoli, EF Kauffmann, F Asta, M Ginesini, C Gianfaldoni, F Vistoli, U Boggi
Presenter: Niccolò Napoli MD | University of Pisa, Italy

Background: Recently, a threshold of 22 cases per year have been demonstrated for improving outcomes after robotic pancreaticoduodenectomy (R-PD) (JAMA Surg., 2017). In this scenario, a large proficiency-based training program seems essential to facilitate a safe implementation of this procedure. However, not all R-PDs have the same level of difficulty and knowing it before the surgery could be fundamental in this context.
The aim of this study was to develop a prediction formula in order to classify each patient undergoing to R-PD for its difficulty level.

Methods: The potentially most important preoperative parameters in determining the difficulty of R-PD were evaluated by a group of international experts through an online survey promoted by the "International Consortium of Minimally Invasive Pancreatic Surgery". The importance of each parameter resulted from the mean of the judgments of the experts who could assign from 0 to 5 points to each of them. By evaluating the presence of each parameter in patients undergoing to R-PDs (n= 235) at our institution from 2008 to 2020, we assigned each patient a score (hypothetical difficulty score) given by the sum of the scores of the individual factors. The association between each factor and the hypothetical difficulty score was measured by using Spearman's Rho coefficient. A linear regression model based on the least square method was developed using factors with highest Spearman's Rho as dependent variables and hypothetical difficulty score as independent variable. Then, we developed a prediction formula using the coefficients of statistically significant factors in multivariate analysis as a coefficient of difficulty. Finally, we applied the prediction formula to our patients to calculate for each of them an actual difficulty score (robotic -pAncreatoDuodenectomy DIffiCulTy- ADDICT score) and divided them into three groups of difficulty (high, intermediate and low). A logistic regression between the score and development of severe post-operative complications (Clavien-Dindo>2) was used to internally validate our score.

Results: The results of the survey are shown in figure 1a. The most important factors (coefficients; p) for predicting the difficulty of R-PD were body mass index > 30 kg/m2 for male and 25 for female (0.648; p 2 (0.046; p 10), intermediate (5-10) and low (< 5) difficulty. The robotic ADDICT score was related to the development of severe post-operative complications (= 2.29; p= 0.0019).

Conclusion: The proposed formula allows to distinguish three different levels of difficulty for patient undergoing R-PD associated with a different probability of developing post-operative complications. Nevertheless, an external validation of this formula is mandatory before it can be widely accepted.

Figure 1a – Survey results

Surgeon	Age>60	Male gender	High BMI (>25 in male and >30 in female)	ASA>2	Chronic pancreatitis	Mild acute pancreatitis	Sever acute pancreatitis	Pancreatic cancer	Benign pancreatic tumor	Main pancreatic duct < 4 mm	Previous laparoscopic abdominal procedure	Previous laparotomic abdominal procedure	Jaundice	Percutaneous biliary drainage	Endoscopic biliary drainage	cT scan vein involvment	cT scan arterial involment	Neoadjuvant chemotherapy	Neoadjuvant radioterapy	Tumor size > 5 cm	Head tumor	Uncinate process tumor	Neck tumor	Right hepatic artery from SMA	Patient dissent to blood transfusions	Liver cirrhosis	Portal hypertension	Recurrent cholangitis	Dunbar syndrome	agree
Surgeon 1	3	4	4	4	5	3	5	3	1	4	1	3	1	2	3	5	5	4	5	4	3	5	4	4	5	5	5	4	4	yes
Surgeon 2	2	2	5	4	4	3	5	4	2	3	3	4	1	3	4	4	5	3	3	4	3	4	4	4	3	4	5	4	4	maybe
Surgeon 3	2	3	4	5	3	3	4	3	1	4	1	2	1	2	2	5	5	2	2	3	4	5	3	2	5	5	5	4	3	maybe
Surgeon 4	1	4	4	3	5	1	5	4	1	4	1	3	2	1	2	5	5	1	1	4	3	4	4	4	4	4	5	4	4	yes
Surgeon 5	1	1	4	3	3	4	5	2	1	4	2	3	1	2	3	4	5	3	3	4	2	4	3	4	5	4	5	4	4	yes
Surgeon 6	2	2	5	4	4	2	5	4	2	3	2	4	2	2	4	5	5	4	4	4	4	4	3	4	5	4	5	3	4	maybe
Surgeon 7	2	1	4	4	5	5	5	3	2	3	4	4	2	2	4	5	5	2	4	5	3	4	4	5	5	5	5	5	2	yes
Surgeon 8	3	3	4	3	4	4	5	3	3	3	2	3	2	2	2	5	5	3	4	4	3	3	4	4	2	3	3	3	4	maybe
Surgeon 9	3	4	5	3	5	5	5	4	2	3	3	4	1	3	3	5	3	2	3	4	3	5	4	4	5	5	5	4	3	maybe
Surgeon 10	2	3	3	3	4	3	4	4	2	4	2	4	1	3	3	4	5	3	4	5	2	4	4	4	3	4	5	3	3	yes
Surgeon 11	2	1	4	3	1	2	5	3	1	5	2	4	1	2	2	5	5	3	4	4	2	3	3	2	2	2	5	3	2	no
Surgeon 12	1	1	5	3	4	2	4	3	1	2	1	2	1	2	1	4	5	4	3	2	4	4	2	2	2	3	3	2	3	yes
Surgeon 13	3	3	4	3	5	4	5	3	2	3	3	4	2	2	3	5	5	5	5	4	4	3	3	5	3	4	5	4	3	yes
Surgeon 14	2	3	3	2	4	4	5	2	3	2	2	2	3	3	2	4	4	4	3	4	2	2	3	3	1	4	4	4	3	yes
Surgeon 15	1	3	3	3	4	3	5	2	2	3	2	3	1	2	1	4	5	2	4	3	2	4	2	4	2	4	2	3	2	yes
Surgeon 16	1	4	4	4	3	1	5	3	1	3	1	2	1	1	1	5	5	3	4	5	1	3	2	2	5	5	5	2	5	yes
Surgeon 17	2	3	4	2	3	2	3	3	2	2	1	2	1	3	2	5	5	2	3	4	3	3	5	4	2	5	4	4	3	yes
Surgeon 18	3	3	5	3	5	4	5	4	2	3	3	4	2	3	3	5	5	3	4	5	3	4	4	3	3	3	3	3	3	yes
Surgeon 19	1	2	3	2	2	3	5	1	2	2	1	3	2	2	2	5	5	2	3	3	1	3	2	3	1	3	5	3	3	yes
Surgeon 20	2	1	3	2	2	3	4	2	1	2	2	3	1	2	2	4	5	2	3	2	1	3	2	2	2	2	3	2	3	maybe
Surgeon 21	2	1	3	1	3	2	4	3	1	1	1	2	2	2	2	5	5	2	3	4	3	4	2	2	2	3	3	3	3	yes
Surgeon 22	1	1	4	4	5	3	5	3	2	3	3	4	1	1	1	5	5	3	4	4	3	2	3	4	3	5	5	2	4	yes
Surgeon 23	3	4	5	4	5	3	5	3	3	4	3	4	2	2	4	5	5	4	4	3	3	4	4	4	3	4	4	4	3	yes
Surgeon 24	1	3	4	1	4	3	5	4	4	3	2	4	1	2	2	4	5	2	3	2	4	4	4	1	4	5	5	2	3	no
Surgeon 25	3	3	5	3	4	4	5	4	2	4	2	4	2	2	2	4	5	3	3	4	3	4	3	4	3	5	4	4	4	yes
Surgeon 26	1	1	3	3	4	2	3	4	2	4	2	3	1	2	2	5	5	5	5	4	3	4	4	2	3	4	5	3	3	yes
Surgeon 27	1	3	3	1	4	4	3	3	1	2	2	3	1	1	1	4	5	2	3	3	1	2	3	2	4	3	3	2	1	yes
Surgeon 28	4	1	4	3	5	4	5	4	2	4	2	4	3	1	2	5	5	3	4	2	3	4	3	4	4	5	5	3	4	yes
Surgeon 29	1	2	4	4	2	1	5	3	1	4	2	3	1	2	1	5	5	4	4	3	2	3	4	2	1	4	4	3	3	maybe
Surgeon 30	4	2	4	3	5	4	5	4	2	2	3	4	2	2	3	4	5	1	2	3	3	5	5	3	2	4	4	3	4	yes
Surgeon 31	1	3	5	3	5	4	5	3	3	3	1	4	1	2	2	5	5	4	5	5	2	4	3	3	3	4	5	1	1	yes
Surgeon 32	3	3	3	4	3	4	5	3	4	4	3	3	2	3	3	5	5	3	3	5	3	4	5	4	4	4	4	3	3	yes
Total	2,0	2,4	4,0	3,0	3,9	3,1	4,7	3,2	1,9	3,1	2,0	3,3	1,5	2,1	2,3	4,7	4,9	2,9	3,5	3,7	2,7	3,7	3,4	3,3	3,2	4,0	4,3	3,2	3,2	
	F3	F3	F1	F2	F2	F2	F1	F2	F4	F2	F3	F2	F4	F3	F3	F1	F1	F3	F2	F2	F3	F2	F2	F2	F2	F1	F1	F2	F2	

Figure 1b – Prediction formula

24.194302602

- 3.343136789 * (0 if *main pancreatic duct < 4 mm*; 1 *if not*)
- 5.039505405 * (0 *if high BMI*; 1 *if not*)
- 3.79554499 * (0 *if cT scan vein involvement*; 1 *if not*)
- 3.864031917 * (0 *if uncinate process tumor*; 1 *if not*)
- 3.560625426 * (0 *if ASA>2*; 1 *if not*)
- 3.030208391 * (0 *if right hepatic artery from SMA*; 1 *if not*)

28. IMPACT OF NEOADJUVANT CHEMORADIATION ON OUTCOMES FOR PATIENTS WITH LOCALIZED PANCREATIC CANCER: A MULTI-INSTITUTIONAL ANALYSIS

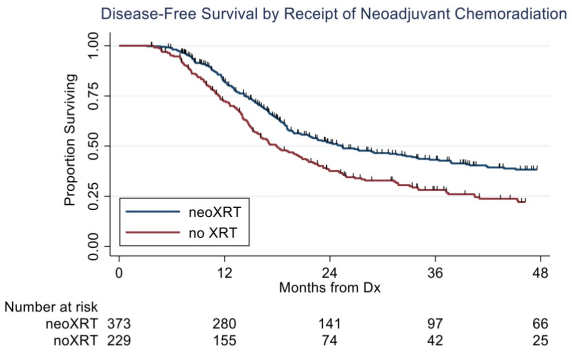
EP Ward, A Paniccia, M Aldakkak, WA Hall, BA Erickson, KK Christians, KK Lee, DB Evans, AH Zureikat, S Tsai
Presenter: Erin Ward MD | Medical College of Wisconsin, United States

Background: Although neoadjuvant therapy for pancreatic cancer (PC) is becoming more widely accepted, the role of neoadjuvant chemoradiation (cXRT) remains controversial. We evaluated the impact of neoadjuvant chemoradiation on disease recurrence.

Methods: Patients who completed neoadjuvant therapy and surgery for operable PC between 2010-2020 were identified from two academic medical centers. Neoadjuvant therapy consisted of chemotherapy alone, chemotherapy followed by cXRT, or cXRT alone; patients were categorized based on the receipt of cXRT. Patients who received postoperative radiation were excluded (n=41). We analyzed pathologic outcomes, patterns of first disease recurrence, disease-free survival (DFS) and overall (OS) from date of diagnosis.

Results: We evaluated 606 patients with operable PC who completed neoadjuvant therapy and surgery; 374 (62%) patients received preoperative cXRT and 232 (38%) did not. The two populations did not significantly differ in terms demographics, tumor size or resectablity ($p>0.05$). Margin positive (R1) resections were observed in 50 (13%) of the 374 patients who received cXRT and 57 (25%) of the 232 patient who did not ($p <0.001$). Node positive disease was present in 137 (37%) of the 374 patients who received cXRT and 161 (69%) of the 232 patients who did not ($p<0.001$). At a median follow-up of 27 months, disease progression was observed in 202 (54%) of the 374 patients who received cXRT and 161 (69%) of the 232 patients who did not ($p <0.001$). Local recurrence occurred in 24 (6%) of the patients who received cXRT and 49 (21%) of patients who did not ($p<0.001$). Median DFS was 22 months among all 606 patients; 25 months for the 375 patients who received cXRT and 18 months for the 232 who did not ($p<0.001$). Preoperative cXRT was also found to be protective for DFS on multivariate analysis, controlling for resectablity, R1 resections and abnormal CA19-9 (HR 0.79, CI 0.64-0.99). Median OS for the entire cohort was 39 months; 40 months for the 375 patients who received chemoradiation and 37 months for the 232 who did not ($p =0.46$).

Conclusion: Neoadjuvant cXRT is associated with lower rates of R1 resections, node positive disease, improved local control and DFS, but comparable OS. As median OS continues to increase (more effective systemic therapy), the impact of local disease control on OS may become more apparent.


Disease-Free Survival by Receipt of Neoadjuvant Chemoradiation
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
neoXRT
no XRT
0
12
24
36
48
Months from Dx
Number at risk
neoXRT 373 280 141 97 66
noXRT 229 155 74 42 25

29. NEOADJUVANT THERAPY IS ASSOCIATED WITH IMPROVED SURVIVAL IN DISTAL PANCREATIC ADENOCARCINOMA

A Chopra, I Nassour, S Al Masri, A DeSilva, N Bahary, A Singhi, K Lee, AH Zureikat, A Paniccia
Presenter: Asmita Chopra MD | University of Pittsburgh Medical Center, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) involving the distal pancreas is associated with late presentation and early metastasis. The use of neoadjuvant therapy (NAT) in distal PDAC remains limited and understudied. We aimed to characterize utilization patterns of NAT and its impact on the prognostic factors, recurrence, and survival of patients with PDAC.

Methods: A single-center, retrospective analysis of patients with distal PDAC, who underwent distal pancreatectomy between 2008 and 2019, was performed. Patients were stratified based on treatment sequence as NAT or surgery first (SF). ANOVA (analysis of variance), Fisher-exact test, and Chi-square test were used to compare outcomes. Disease-free survival (DFS) and overall survival (OS) were estimated using Kaplan-Meier curves and Cox-regression analysis.

Results: A total of 144 patients (mean age 68 years, 56% females) were included in the study; 62 (43%) received NAT, and 82 (57%) underwent SF. Patients receiving NAT were significantly younger (65 vs. 70 years, p=0.002) with a higher incidence of borderline-resectable disease (21 vs. 2%, p<0.001) than those undergoing SF. The NAT group had a higher percentage of pancreatic neck and body tumors compared to the SF group (10 vs. 1% and 61 vs. 49% respectively, p=0.007). On survival analysis, patients receiving NAT had significantly higher DFS (20 vs. 15 months; HR=0.631, p=0.042) and OS (45 vs. 30 months; HR=0.491, p=0.004), compared to patients undergoing SF.

Conclusion: NAT is associated with a significant delay in recurrence and improvement in overall survival rates following distal pancreatectomy for PDAC. These findings warrant further validation in prospective studies.

Table 1: Cox- regression analysis for overall survival and disease free survival

VARIABLE	HAZARD RATIO	95% CI	P-VALUE
OVERALL SURVIVAL			
NAT	0.491	0.302- 0.799	0.004
Vascular resection	2.416	1.120-5.211	0.025
CCI age-adjusted	1.181	1.058- 1.319	0.003
AJCC 8TH (I =reference)			
Stage II	1.200	0.641- 2.246	0.568
Stage III	2.177	1.062- 4.464	0.034
LVI	2.816	1.407- 5.638	0.003
Adjuvant chemotherapy	0.454	0.274- 0.754	0.002
DISEASE FREE SURVIVAL			
NAT	0.637	0.412- 0.984	0.042
Age	0.962	0.940-.0985	0.001
CCI age- adjusted	1.278	1.126-1.450	<0.001
LVI	2.145	1.2698- 3.544	0.003

Abbreviations: NAT, Neoadjuvant Therapy; CI, Confidence interval; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer; LVI, Lymphovascular invasion

30. AN EVALUATION OF ADJUVANT CHEMOTHERAPY FOLLOWING NEOADJUVANT CHEMOTHERAPY AND RESECTION FOR BORDERLINE RESECTABLE AND LOCALLY ADVANCED PANCREATIC CANCER

C Zhang, R Wu, LM Smith, M Baine, C Lin, BN Reames
Presenter: Chunmeng Zhang MD | University of Nebraska Medical Center, United States

Background: Multiagent chemotherapy is universally accepted as the preferred initial management of patients with borderline resectable and locally advanced pancreatic cancer (BRLA). However, after neoadjuvant therapy (NAT) and resection, the role of adjuvant therapy (AT) is poorly understood. This study sought to investigate the impact of AT on overall survival (OS) in BRLA patients who received NAT.

Methods: Using the National Cancer Database (NCDB) between 2011-2017, we identified patients with pancreatic ductal adenocarcinoma (PDAC) with T4, N0-1, M0 disease who received NAT and curative-intent surgical resection. Kaplan-Meier method was used to estimate OS and log rank tests were performed to test the homogeneity of OS across strata. A multivariate Cox proportional hazards regression was performed to examine the association between AT and OS after adjusting for relevant patient, disease, and treatment-related characteristics. Interaction terms were used to further investigate the relationship between AT and pathological outcomes such as nodal and margin status.

Results: Of 17,905 patients with BRLA identified in the 7-year period, 764 received NAT and curative-intent surgical resection, of which 203 received AT. Median age at diagnosis was 64 years, 47% were male, median year of diagnosis was 2015, and the average NAT duration was 117 days. Kaplan Meier analysis revealed no differences in median OS between AT vs non-AT groups (29.0 vs 27.7 months, $p = 0.93$). In the multivariate Cox proportional hazards model, interaction between margin status and AT was marginally significant ($p = 0.07$). After adjusting for other demographic and clinicopathologic factors, when margin was positive, AT was associated with an improved survival (HR 0.54, 95%CI 0.32-0.90, $p=0.03$). No significant interactions between AT and NAT duration or nodal status were identified ($p>0.2$). Other factors independently associated with OS include age (HR 1.02, 95% CI 1.01-1.03, p 75th percentile (HR 1.61, 95% CI 1.23-2.11, $p < 0.001$), and positive nodal status (HR 1.62, 95% CI 1.28-2.06, $p < 0.001$). Recent diagnosis (2015-2017) was marginally significant (HR 0.79, 95% CI 0.62-1.00, $p=0.05$). Use of radiation, NAT duration, and type of treatment center were not associated with OS.

Conclusion: AT was not associated with survival in BRLA patients who received NAT and curative-intent surgical resection, though subgroup analysis suggests AT was associated with prolonged survival for BRLA patients with positive margins on surgical pathology. Further research is necessary to better understand the role of AT following NAT in patients with BRLA.

31. PROPHYLACTIC PERIOPERATIVE ANTIBIOTICS IN OPEN PANCREATICODUODENECTOMY: WHEN LESS IS MORE, AND WHEN IT'S NOT. A NSQIP PROPENSITY MATCHED ANALYSIS

S Naffouje, K Allenson, P Hodul, M Malafa, J Pimiento, D Anaya, A Dam, J Klapman, J Fleming, J Denbo
Presenter: Samer Naffouje MD | Moffitt Cancer Center, United States

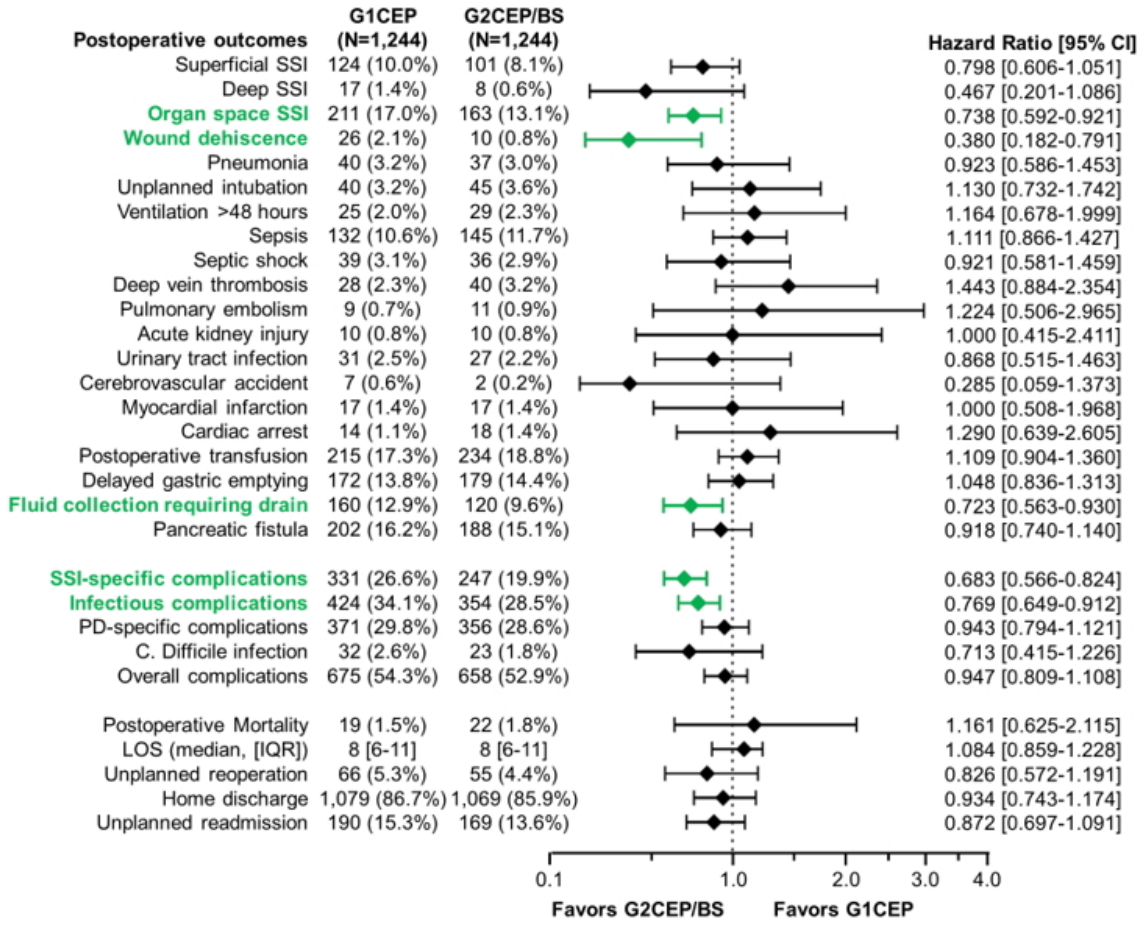
Background: We hypothesized that first-generation cephalosporins (G1CEP) provide adequate antimicrobial coverage for pancreaticoduodenectomy (PD) when no biliary stent is present, but might be inferior to second-generation cephalosporins or broad-spectrum antibiotics (G2CEP/BS) in decreasing surgical-site infections (SSI) rates when a biliary stent is present.

Methods: NSQIP 2014-2019 was used to select patients who underwent elective open PD. We divided the population into no-stent vs. stent groups based on the status of biliary drainage, then divided each group into G1CEP vs. G2CEP/BS subgroups based on the choice of perioperative antibiotics. We matched the subgroups per a propensity score match and analyzed postoperative outcomes.

Results: 6,245 cases out of 39,779 were selected; 2,821 in the no-stent (45.2%) vs. 3,424 (54.8%) in the stent group. G1CEP were the antibiotics of choice in 2,653 (42.5%) vs. G2CEP/BS in 3,592 (57.5%) cases. In the no-stent group, we matched 1,129 patients between G1CEP and G2CEP/BS. There was no difference in SSI-specific complications (20.3% vs. 21.0%; p=0.677), general infectious complications (25.7% vs. 26.9%; p=0.503), PD-specific complications, overall morbidity, length of stay (LOS), or mortality. In the stent group, we matched 1,244 pairs. G2CEP/BS had less SSI-specific complications (19.9% vs. 26.6%; p<0.001), collections requiring drainage (9.6% vs. 12.9%; p=0.011), and general infectious complications (28.5% vs. 34.1%; p=0.002), but no difference in overall morbidity, mortality, LOS, and readmission rates.

Conclusion: G2CEP/BS are associated with reduced rates of SSI-specific and infectious complications in stented patients undergoing open elective PD. In patients without prior biliary drainage, G1CEP provides adequate antimicrobial coverage.

Figure: Forest plot for hazard ratios of postoperative outcomes for matched patients who underwent open PD procedure **with stent**. **CI**: Confidence Interval; **C. Difficile**: Clostridium Difficile; **G1CEP**: 1st Generation Cephalosporin; **G2CEP/BS**: 2nd Generation Cephalosporin or Broad Spectrum; **IQR**: Interquartile Range; **LOS**: Length of stay; **PD**: Pancreaticoduodenectomy; **SSI**: Surgical Site Infection.



32. A PROPENSITY-MATCHED ANALYSIS OF THE POSTOPERATIVE VENOUS THROMBOEMBOLISM RATE AFTER PANCREATODUODENECTOMY BASED ON OPERATIVE APPROACH

JJ Hue, K Sugumar, MJ Beckman, MR Driedger, LD Rothermel, JM Hardacre, JB Ammori, JM Winter, LM Ocuin

Presenter: Jonathan Hue MD | University Hospitals Cleveland Medical Center, United States

Background: In recent years, a greater proportion of complex operations, including pancreatoduodenectomy, are being attempted via minimally invasive techniques, often at the expense of prolonged operative times. This raises the question if patients undergoing minimally invasive pancreatoduodenectomy are at a greater risk of postoperative VTE, as compared to a traditional open operation. We aimed to compare venous thromboembolism (VTE) rates after open and minimally invasive pancreatoduodenectomy using an administrative dataset.

Methods: Patients who underwent pancreatoduodenectomy within the National Surgical Quality Improvement Program targeted pancreatectomy database (2016-2018) were identified. The VTE rate, including both deep vein thrombosis (DVT) and pulmonary embolism (PE), was compared between patients who underwent open or minimally invasive pancreatoduodenectomy directly and after propensity score matching 1:1 for demographics, comorbidities, and peri-/intra-operative factors. Multivariable models were used to account for confounding.

Results: A total of 12,227 patients underwent pancreatoduodenectomy during the study period (open: n=11,217; minimally invasive: n=1,010). Before matching, the VTE rate was higher among patients who underwent minimally invasive pancreatoduodenectomy (5.2% vs. 3.8%, p=0.033), and minimally invasive resection was independently associated with VTE on multivariable logistic regression (odds ratio (OR)=1.46, 95% confidence interval (CI)=1.09-2.06). Additional risk factors associated with higher VTE risk include obesity, receipt of perioperative transfusions, and prolonged operative times. There were no differences between the minimally invasive and open cohorts in the number of days from surgery until diagnosis of DVT (12 vs. 11 days, p=0.471) or PE (8 vs. 9 days, p=0.214). Patients who experienced a postoperative VTE were more likely to be re-intubated (OR=4.69, 95% CI 3.51-6.24), suffer a stroke (OR=6.89, 95% CI 3.13-15.2), suffer a myocardial infarction (OR=5.23, 95% CI 3.37-8.12), suffer cardiac arrest (OR=3.77, 95% CI 2.28-6.24), and die within 30 days of surgery (OR=4.07, 95% CI 2.66-6.23).

After matching, there were 916 patients per group without differences in demographics or comorbidities. Patients who underwent minimally invasive pancreatoduodenectomy had longer median operative times as compared to an open approach (422 vs. 348 minutes). The VTE rate remained higher following minimally invasive pancreatoduodenectomy after matching (5.1% vs. 2.9%, p=0.018), mainly driven by a higher DVT rate (3.9% vs. 1.7%, p=0.005).

Conclusion: Minimally invasive pancreatoduodenectomy is associated with a higher likelihood of postoperative VTE compared to open surgery. Further study is needed, but there may be rationale to design specific VTE risk reducing interventions based on the number of risk factors present. The risks of VTE prophylaxis would have to be weighed against risks of post-pancreatectomy hemorrhage.

33. DISPARITIES IN REFERRAL OF PATIENTS WITH PANCREATIC NEOPLASMS DURING COVID19

JP Lever, CH Mullins, SM Vickers, TN Wang, JB Rose, S Reddy
Presenter: Marvi Tariq MD | University of Alabama at Birmingham, United States

Background: Pancreatic cancer is a deadly disease, with most patients requiring referral to a tertiary care center for expert evaluation. During the COVID19 pandemic, access to healthcare has become limited, and disproportionately so for vulnerable socioeconomic demographics. We sought to examine the effect of the COVID19 pandemic on pancreatic neoplasm referrals and subsequent therapy in Alabama.

Methods: A retrospective analysis of patients presenting with pancreatic mass to a high-volume tertiary care hospital was performed. Time intervals were chosen as follows: 07/01/2019-12/31/2019 (pre-COVID19) and 04/01/2020- 09/30/2020 (COVID19). Each patient was evaluated in a multidisciplinary clinic and tumor board prior to initiating therapy. Sociodemographic and clinical characteristics were compared.

Results: A total of 109 patients were included (pre-COVID19 n=68, COVID19 n=41). Both groups showed similar demographic characteristics (pre-COVID19 vs COVID19) including age (mean 66 vs. 67 years, P=0.73), sex (%Female, 46% vs. 49%,P=0.90), insurance type (%Commercial 53% vs. 56%,P=0.42), and median income ($51,185 vs. 55,193, P=0.64). However, race significantly affected the referral patterns during COVID19, with the percentage of Caucasians increasing from 77% to 97% of all referrals during COVID (p=0.013).

Conclusion: COVID pandemic disproportionately affected referrals of people of color, with Caucasians comprising 97% of all pandemic referrals. As the COVID19 pandemic persists, efforts must be made to ensure equity in patient referrals and ensure timely and appropriate care to all patient populations regardless of race.

	Pre-COVID	Post-COVID	p-value
	N= 68	N=41	
Age, years (mean + SD)	65.6 (+/- 14.1)	66.5 (+/- 11.9)	0.729
Female (%)	31 (45.5%)	20 (48.7%)	0.900
Race, Caucasian (%)	50 (76.9%)	37 (97.3%)	**0.013***
Insurance, Commercial (%)	36 (52.9%)	23 (56.1%)	0.424
BMI (mean +/- SD)	27.1 +/- 5.4	28.3 +/- 6.1	0.307
Income (by zip code), median	51,185	55,913	0.638

34. EARLY RECOGNITION AND MANAGEMENT OF COMPLICATIONS AFTER PANCREATIC SURGERY

FJ Smits, AC Henry, MG Besselink, OR Busch, CH van Eijck, M Arntz, TL Bollen, OM van Delden, D van den Heuvel, C van der Leij, KP van Lienden, A Moelker, BA Bonsing, IH Borel Rinkes, K Bosscha, RM van Dam, WJM Derksen, M den Dulk, S Festen, B Groot Koerka

Presenter: Anne Claire Henry | Regional Academic Cancer Center Utrecht, Netherlands

Background: Early recognition and management of postoperative complications, before they become clinically manifest, may improve outcomes of surgical patients, especially in high-risk procedures such as pancreatic resection.

Methods: We conducted a nationwide stepped-wedge cluster randomized trial. All patients undergoing pancreatic resection over a 22-month period in The Netherlands were included. 17 centers were randomized for time to crossover from usual care (control group) to treatment according to a multimodal, multidisciplinary algorithm for early recognition and minimally invasive management of postoperative complications (intervention group). The algorithm included daily evaluation of clinical and biochemical markers. It determined when to perform abdominal computed tomography, radiologic drainage, start antibiotic treatment and remove abdominal drains. The primary end-point was a composite of bleeding requiring invasive intervention, organ failure, and 90-day mortality.

Results: 1748 patients were included. The primary end-point occurred in 73 of 863 patients (8.5%) in the intervention group and in 124 of 885 patients (14.0%) in the control group (adjusted odds ratio 0.42, 95% confidence interval [CI] 0.27 to 0.66, P < 0.001). There was a decrease in organ failure (4.5% vs. 10.3%, adjusted odds ratio 0.30, 95%CI 0.18 to 0.50, P < 0.001) and a lower 90-day mortality (2.7% vs. 5.0%, adjusted odds ratio 0.38, 95%CI 0.18 to 0.82, P=0.01) in patients treated according to the algorithm.

Conclusion: The algorithm for early recognition and minimally invasive management of complications after pancreatic resection reduced the composite end-point of bleeding requiring invasive intervention, organ failure and death, as compared to usual care. This included an approximate 50% reduction of nationwide mortality.

35. PSYCHOSOCIAL DISTRESS IN MALIGNANCY: A COMPREHENSIVE INVESTIGATION OF INCIDENCE, DISTRESS SUBTYPES, NATURAL HISTORY, AND ASSOCIATED ONCOLOGIC OUTCOMES

TL Sutton, M Affi-Koprowski, A Grossblatt-Wait, S Brown, G McCarthy, B Liu, A Gross, C Macuiba, S Hedlund, J Brody, BC Sheppard

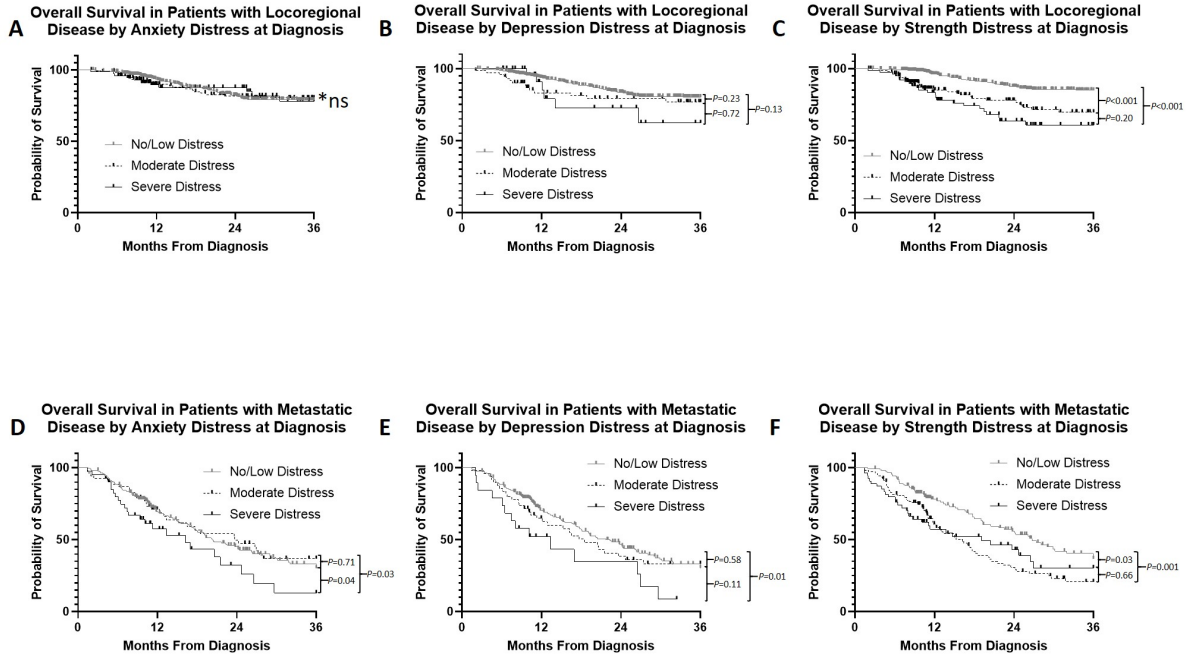
Presenter: Thomas Sutton MD | Oregon Health & Science University, United States

Background: Psychosocial distress in cancer patients is an under-studied and under-screened clinical entity with the potential for impact on patient treatment decisions, compliance, and disease trajectory. To date, no studies have investigated the complex interplay of distress subtypes, risk factors, natural history, and impact on oncologic outcomes across the full spectrum of malignancies, including hepato-pancreato-biliary (HPB) cancers. We sought to characterize the incidence and natural history of psychosocial distress in cancer, and evaluate risk factors and associations with oncologic outcomes.

Methods: We performed a retrospective cohort study for patients seen at medical, surgical, and radiation oncology clinics at our institution from 2010-2020. Eligible patients were offered screening for psychosocial distress at their second oncology visit and every 6 months thereafter. Distress was assessed for eight categories: anxiety, depression, insurance/financial, family, memory, strength, weight loss, and any distress. Distress at each timepoint was categorized as none, low, moderate, or severe based on category-specific thresholds. Multivariable logistic regression was utilized to evaluate factors associated with distress in the eight categories. Kaplan-Meier analysis using the log-rank test and multivariable Cox proportional hazards modeling were utilized to investigate associations of distress at diagnosis with overall survival (OS).

Results: 5660 patients were included in the study; forty-one percent of patients (n=2327) responded to two or more longitudinal distress surveys; a total of 9981 survey responses were collected. The response rate was 43.2% (n=13090 potential respondents), clinicopathologic differences between responders and non-responders were minor. Distress was highest at the time of diagnosis for most distress categories, progressively declining until 18 months following diagnosis, followed by a consistent level of distress thereafter up to ten years following diagnosis. HPB cancers had the highest overall distress of all disease sites.
On Kaplan-Meier analysis of patients with solid tumors, degree of anxiety and depression distress was not associated with OS in patients with locoregional disease (Figure, Panel A-B); both moderate and severe strength distress were associated with inferior OS (Figure, Panel C). In patients with metastatic disease at diagnosis, degree of anxiety, depression, and strength distress was associated with OS (Figure, Panel D-F). On multivariable analysis controlling for relevant prognostic factors (disease site, SEER stage, and patient age), high anxiety or depression distress at diagnosis was independently associated with worse OS (HR 1.49, 95% CI 1.50-2.11, P=0.02), but high strength distress was not (HR 1.32, 95% CI 0.97-1.81, P=0.08). Insurance/financial distress, family distress, and memory distress were not associated with OS.
Risk factors for distress at diagnosis varied by distress category, and included age, gender, disease site, disease stage, payor, and estimated patient income. Most patients with initially severe distress generally improved with time, however 5-10% of patients with initially low distress progressed to severe distress within 12 months, depending on category.

Conclusion: Psychosocial distress is high in HPB malignancies, and is a constantly-evolving entity responsive to both oncologic and life events. Distress presents a major burden that is frequently under-addressed, and longitudinal distress screening has immense value, allowing tailored patient evaluation and referral to specialists as clinically indicated.


A
Overall Survival in Patients with Locoregional Disease by Anxiety Distress at Diagnosis
B
Overall Survival in Patients with Locoregional Disease by Depression Distress at Diagnosis
C
Overall Survival in Patients with Locoregional Disease by Strength Distress at Diagnosis
D
Overall Survival in Patients with Metastatic Disease by Anxiety Distress at Diagnosis
E
Overall Survival in Patients with Metastatic Disease by Depression Distress at Diagnosis
F
Overall Survival in Patients with Metastatic Disease by Strength Distress at Diagnosis
Probability of Survival
Months From Diagnosis
No/Low Distress
Moderate Distress
Severe Distress
*ns
P=0.23
P=0.72
P=0.13
P<0.001
P=0.20
P<0.001
P=0.71
P=0.04
P=0.03
P=0.58
P=0.11
P=0.01
P=0.03
P=0.66
P=0.001

36. PREOPERATIVE RISK STRATIFICATION OF POSTOPERATIVE PANCREATIC FISTULA: TRAINING AND EXTERNAL VALIDATION OF A RISK-TREE PREDICTIVE MODEL FOR PANCREATODUODENECTOMY

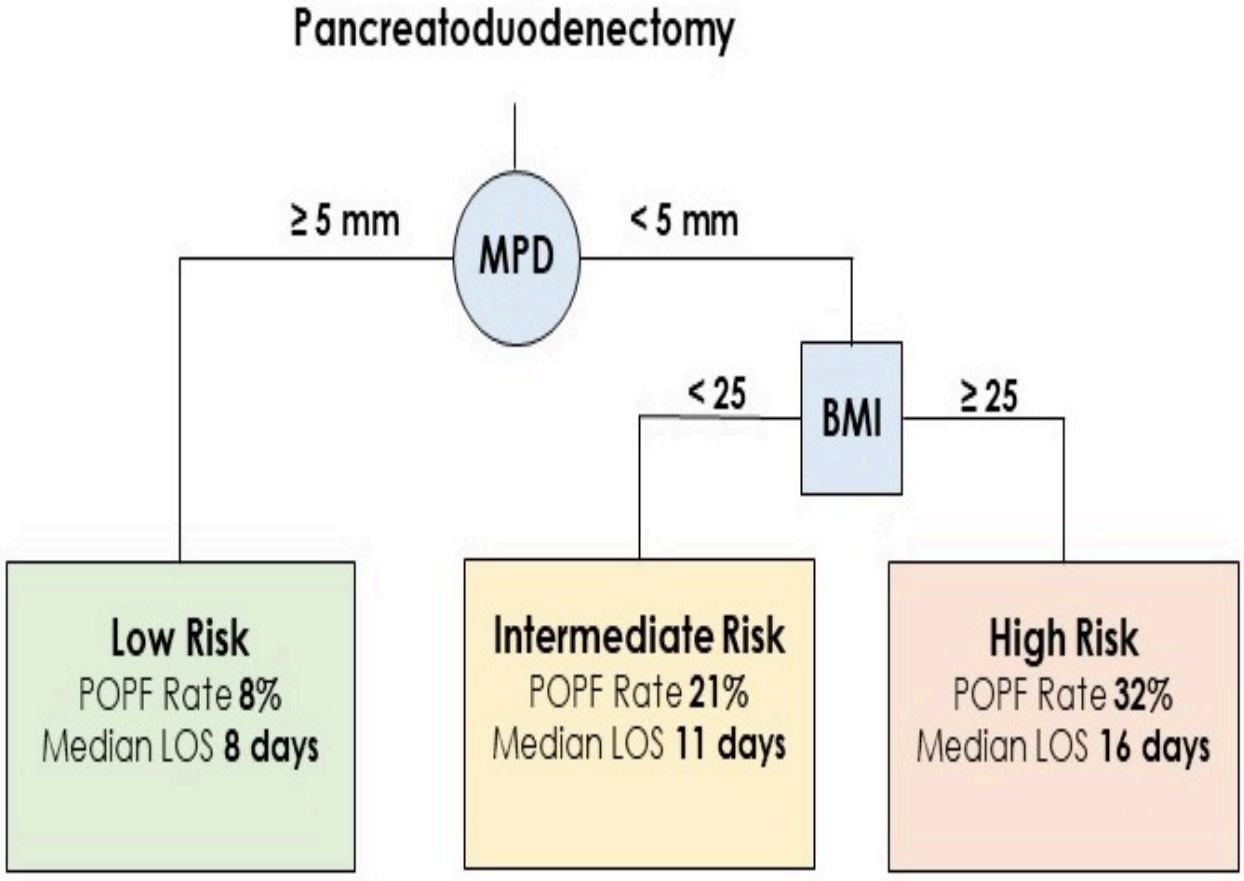
G Perri, G Marchegiani, S Partelli, S Crippa, B Bianchi, L Cinelli, A Esposito, N Pecorelli, M Falconi, R Salvia
Presenter: Giampaolo Perri MD | University of Verona, Italy

Background: Existing postoperative pancreatic fistula (POPF) risk scores rely on intraoperative parameters, limiting their value in the preoperative setting. A preoperative predictive model to stratify the risk of developing POPF before pancreatoduodenectomy (PD) was built and externally validated.

Methods: A regression risk-tree model for preoperative POPF risk stratification was developed in the Verona University Hospital training cohort using preoperative variables and then tested prospectively in a validation cohort of patients who underwent PD at San Raffaele Hospital of Milan.

Results: In the study period 566 (training cohort) and 456 (validation cohort) patients underwent PD. In the multivariate analysis BMI, radiographic main pancreatic duct (MPD) diameter and ASA score ≥3 were independently associated with POPF. The regression tree analysis allocated patients into three preoperative risk groups with an 8%, 21% and 32% risk of POPF (all P < 0.01) based on MPD diameter (≥ or < 5 mm) and BMI (≥ or < 25). The three groups were labeled low, intermediate, and high risk and consisted of 206 (37%), 188 (33%) and 172 (30%) patients, respectively. The risk-tree was applied to validation cohort, successfully reproducing three risk groups with significantly different POPF risks (all P < 0.01).

Conclusion: In candidates for PD, the risk of POPF can be quickly and accurately determined in the preoperative setting based on the BMI and MPD diameter at radiology. Preoperative risk stratification could potentially guide clinical decision-making, improve patient counseling, and allow the establishment of personalized preoperative protocols.



37. SERUM VERSUS DRAIN FLUID AMYLASE: WHICH BETTER PREDICTS PANCREATECTOMY OUTCOMES?

BC Brajcich, RM Platoff, VM Thompson, B Hall, CY Ko, HA Pitt
Presenter: Brian Brajcich MD, MS | American College of Surgeons, United States

Background: Postoperative hyperamylasemia (POHA) has been proposed as a predictor of complications following pancreatectomy. However, the prognostic utility of a grading schema for POHA as well as a comparison with drain fluid amylase have not been evaluated. Our objectives were to (1) evaluate the association of a grading schema for POHA with postoperative pancreatic fistula (POPF) and other postoperative outcomes, and (2) compare the prognostic utility of POHA with postoperative day 1 drain fluid amylase (DFA-1).

Methods: Patients who underwent pancreatoduodenectomy or distal pancreatectomy were identified in the ACS NSQIP pancreatectomy-targeted dataset from January 2019 through March 2020. Patients who met criteria for POHA, defined as an elevated serum amylase concentration above the upper limit of normal on postoperative day 0 or 1, were assigned to grade A, grade B, or grade C based on the presence of additional sequelae. The primary outcome was clinically relevant (grade B or C) POPF (CR-POPF) within 30 days. Secondary outcomes included death or serious morbidity, organ space surgical site infection (SSI), percutaneous drainage, reoperation, prolonged length of stay (LOS) ≥14 days, and unplanned readmission. Multivariable logistic regression models were constructed to evaluate the association of POHA grade with the primary and secondary outcomes. C-statistics of logistic regression models including POHA and DFA-1 were compared to assess the prognostic utility of these two postoperative markers.

Results: POHA was identified in 520 patients at 98 hospitals, of whom 261 (50.2%) had grade A, 234 (45.0%) had grade B, and 25 (4.8%) had grade C POHA. The overall rate of CR-POPF was 42.7%, which is 3 times the incidence seen among the overall NSQIP population of patients who undergo pancreatectomy. CR-POPF was higher among patients with grade B (66.2%, OR 9.28, 95% CI 5.84-14.73, p<0.001) and C (68.0%, OR 10.50, 95% CI 3.77-29.26, p<0.001) compared with grade A POHA (19.2%, reference). Rates of death or serious morbidity, organ space SSI, percutaneous drain placement, reoperation, prolonged LOS, and readmission were increased for grade B and C POHA (Table). The odds of an optimal outcome without any of the aforementioned events was significantly lower among patients with grade B or C POHA. Models including POHA data were superior at predicting CR-POPF than models with DFA-1 (c-statistic: 0.802 vs. 0.704, p<0.002) and models containing both predictors were better than those with POHA data alone (c-statistic: 0.822 vs. 0.802, p=0.039).

Conclusion: The grade of postoperative hyperamylasemia (POHA) is an important predictor of outcomes following pancreatectomy. POHA outperforms drain fluid amylase on postoperative day 1 in predicting postoperative pancreatic fistula. Routine postoperative measurement of serum amylase should be added to care pathways, and a formalized grading schema for postoperative hyperamylasemia should be developed.

Table. Postoperative Hyperamylasemia Grade and Postoperative Outcomes

	Grade A (N = 261)		Grade B (N = 234)		Grade C (N = 25)	
	%	Odds ratio	%	Odds ratio	%	Odds ratio
CR-POPF	19.2		66.2	9.28*	68.0	10.50*
Death or serious morbidity	21.8		58.6	5.11*	80.0	13.88*
Organ space SSI	14.6		49.6	6.26*	68.0	13.54*
Percutaneous drain	9.2	1	46.2	8.86*	56.0	13.14*
Reoperation	3.8	Reference	10.3	2.59*	68.0	46.69*
Prolonged LOS ≥14 days	10.8		42.5	7.08*	45.0	5.86*
Readmission	16.9		31.2	2.54*	32.0	2.82†
Optimal outcome‡	63.2		15.4	0.09*	12.0	0.07*

** $p < 0.01$*

† $p < 0.05$

‡ Defined as the absence of postoperative complications, percutaneous drainage, readmission, reoperation, or prolonged LOS

38. DRAIN VERSUS NO DRAIN AFTER DISTAL PANCREATECTOMY: A PROPENSITY SCORE MATCHED MULTICENTER ANALYSIS

EA van Bodegraven, M De Pastena, FL Vissers, A Balduzzi, G Malleo, G Marchegiani, J Stauffer, OR Busch, R Salvia, J van Hilst, C Bassi, MG Besselink, HJ Asbun
Presenter: Ward van Bodegraven MD | Amsterdam UMC, Netherlands

Background: Post-operative pancreatic fistula (POPF) remain the most common complication after distal pancreatectomy (DP). Placement of a surgical drain could be beneficial for early detection of pancreatic leakage and hemorrhage but could actually also facilitate POPF and infection. This study aimed to compare outcomes between drain or no drain placement.

Methods: An international retrospective cohort study in consecutive patients after DP in one American (selective drainage (SDG)) and two European (routine drainage (RDG)) centers (2010-2019). Primary outcome was Clavien-Dindo≥3 complications and POPF grade B/C. Propensity score matching was performed for drain placement. Univariable and multivariable analyses were performed to evaluate postoperative outcomes.

Results: 966 patients had DP in the study period of which 805 (83%) had a drain. Propensity score matching was possible in 74 patients. Drain and no drain groups were similar with respect to pre- and peroperative parameters. The rate of POPF B and C (4.1% vs 16.2% p<0.05), Clavien-Dindo≥3 complications (8.1% vs 18.9% p=0.05), and readmission (4.1%vs14.9% p<0.05) was lower in the no drain group. The hospital stay was shorter in the no drain group (median 3 vs 7 days p<0.001). The rates of percutaneous drainage (5.4% vs 12.2% p=0.147), reoperations (1.4% vs 2.7% p=0.56) and 30-day mortality (0% vs 1.4% p=0.316) were comparable. In multivariable analysis, omitting a drain was still significant with a decreased risk POPF (OR: 0.218 CI: 0.059 - 0.809 p<0.05).

Conclusion: This retrospective study found lower POPF, major complications and readmissions and shorter hospital stay in the no drain group. Based on these results we initiated the binational PANDORINA trial where the impact of a omitting a drain is compared with a drain in a highly standardized surgical technique setting.

39. DRAIN VERSUS NO-DRAIN AFTER DISTAL PANCREATECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

EA van Bodegraven, T van Ramshorst, A Balduzzi, S Festen, G Marchegiani, OR Busch, R Salvia, C van Eijck, MG Besselink

Presenter: Ward van Bodegraven MD | Amsterdam UMC, Netherlands

Background: Morbidity after distal pancreatectomy (DP) remains high with post-operative pancreatic fistula (POPF) as most common complication. Surgeons have traditionally placed a surgical drain for early detection and treatment of POPF but this drain could actually also facilitate pancreatic leakage and introduce infection. This study aimed to determine the role of routine surgical drainage on POPF and major morbidity after DP.

Methods: A systematic search using PubMed, Embase and Cochrane until Jan 1st 2021. All retrospective and prospective studies comparing routine drainage versus no routine drainage after DP in adults were included. Eligibility criteria of the identified studies were scrutinized to identify excluded subgroups (i.e. patients who always received a routine drain). Quality assessment was done by the Newcastle-Ottawa scale.

Results: Five studies, of which 1 RCT and 4 retrospective studies involving 2153 patients, were included in the review and meta-analysis. Severe complications were found to be significantly lower in the no drain group compared to the drain group (RR 0.82 [0.68, 0.99] $p<0.05$). The occurrence of pancreatic fistula was significantly lower in the no drain group compared to the drain group (RR 0.55 [0.42, 0.72] $p<0.001$). There was no significant difference in radiological interventions, postoperative hemorrhage, reoperations or 30-day mortality.

Conclusion: Routine drain placement should be reconsidered since severe complications and CR-POPF are lower in the pooled patients without a drain and drains were not able to decrease the amount of radiological interventions. Patients with a high risk for POPF might benefit from drain but a tool to identify those is lacking. RCTS are needed to confirm these findings.

40. WNT11 PROMOTES EARLY MICROMETASTATIC DISEASE IN PANCREATIC DUCTAL ADENOCARCINOMA

EC Donovan, B Dai, J Deng, X Li, CM Siangco, MP Kim
Presenter: Eileen Donovan MD | University of Texas MD Anderson Cancer Center, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) is a systemic disease characterized by early metastasis, though the drivers of this process remain poorly defined. The non-canonical Wnt-PCP pathway has been implicated as a potential driver of tumor cell dissemination through Wnt ligand-mediated activation of cognate receptors that results in cytoskeleton rearrangements. One non-canonical Wnt ligand, Wnt11, has been previously implicated in metastasis and is associated with decreased disease free survival in PDAC. We tested if Wnt11 significantly affects metastasis in a genetically engineered mouse model of pancreatic cancer.

Methods: Mice with LSL-KrasG12D/+, p53wmR172H/+, and p48-Cre alleles were crossed with and without conditional Wnt11fl/fl alleles to generate cohorts of Wnt11 wildtype and knockout mice in the context of the well-established KPC PDAC mouse model (KPwm/+C, n=22; KPwm/+C; Wnt11fl/fl, n=37). A conditional LSL-ROSA26-tdTomato reporter allele was bred into all mice to identify metastatic disease in distant organs. Mice were sacrificed when euthanasia criteria were met, and metastases were identified with whole organ fluorescence microscopy via tdTomato+ lesions. Liver and lung metastases were enumerated and measured with ImageJ. Metastatic lesions were classified by diameter as: 1) micrometastases (< 100 uM); 2) intermediate metastases (100-499 uM) or; 3) macrometastases (≥500 uM).

Results: There were no differences in median overall survival between KPwm/+C and KPwm/+C; Wnt11fl/fl mice (193.5 vs. 193 days, p = 0.83). The histologic appearance of primary pancreatic tumors from KPwm/+C and KPwm/+C; Wnt11fl/fl mice was similar without gross alterations in stromal composition (54.7% vs. 52.8% pan-cytokeratin+, p = 0.62). However, pulmonary micrometastatic disease in mice < 170 days of age at euthanasia was significantly lower in KPwm/+C; Wnt11fl/fl mice relative to KPwm/+C mice (mean number of metastases 83 vs. 1828, p = 0.022). Moreover, while pulmonary metastases in KPwm/+C mice were abundant and diffusely distributed, the lungs of KPwm/+C; Wnt11fl/fl mice contained only scant metastases. No significant differences were observed in the mean number of intermediate-sized (0.5 vs. 27.4, p = 0.17) or macrometastases (0.0 vs 1.6, p = 0.13) between KPwm/+C; Wnt11fl/fl and KPwm/+C mice, respectively. Further, significant differences in metastatic burden were not observed in the liver between KPwm/+C and KPwm/+C;Wnt11fl/fl cohorts (23.2% vs 4.8% metastatic burden/total liver area, p = 0.11).

Conclusion: Wnt11 promotes early pulmonary metastasis with a trend towards the promotion of hepatic metastasis in pancreatic cancer. The role of Wnt11 in PDAC metastasis is context dependent and may be related to factors inherent in the pre-metastatic niche. Further work is needed to better define the effects of stromal secreted Wnt11 in tumor cell dissemination and metastatic outgrowth.

41. EXAMINATION OF WNT SIGNALING AS A THERAPEUTIC TARGET FOR PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) USING A PANCREATIC TUMOR ORGANOID LIBRARY (PTOL)

HH Hawkins, BW Yacob, ME Brown, SM Bagby, SJ Hartman, CD Brindley, WA Messersmith, PJ Dempsey, TM Pitts

Presenter: Hayley Hawkins BS | University of Colorado, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) commonly presents at advanced stages and is refractory to most treatment modalities, making it one of the most lethal cancers. Although the low tumor cellularity and high desmoplastic response convolutes the relationship between genotype and biological phenotypes, gene mutations associated with PDACs have been identified. Wnt pathway mutations are rarely detected in PDAC, but Wnt signaling is activated by pancreatic duct ligation injury and plays a critical role in the proliferation and chemotherapeutic resistance in other cancers. Patient derived pancreatic tumor organoid libraries (PTOL) allow for more accurate investigation of the biological phenotypes that might lead to therapies that further improve survival. This study aims to subclassify PDAC organoids based on Wnt dependency and determine if combinatory treatment with Wnt inhibitors and chemotherapy would serve as a feasible treatment.

Methods: Minimal media conditions required to maintain growth of nine PDAC organoids grown in Human Pancreatic Stem Cell medium was assessed with depletions of various niche factors. For confirmation of Wnt inhibition, organoids grown in minimal media were treated with Wnt inhibitors (ETC-159, ICG001, C59). Select organoids demonstrating Wnt dependency were treated with the Wnt inhibitor ETC-159 as a single agent and in combination with Gemcitabine or Paclitaxel in vitro. Growth was assessed with CellTiter Glo 3D and ANOVA was used for statistical analysis. Organoid lines demonstrating response to combinatory treatment in vitro were assessed in vivo as a matched patient-derived xenograft.

Results: Minimal media conditions, growth factor dependency, and Wnt dependency determined via Wnt inhibition were determined as described above for nine patient derived organoids (PDOs): Panc129, Panc193, Panc268, Panc269, Panc271, Panc272, Panc305, Panc308, Panc320. Panc269 demonstrated a trend of reduced organoid growth when treated with ETC-159 in combination with paclitaxel as compared with paclitaxel alone and ETC-159 alone. This trend was also observed in ETC-159/gemcitabine combination. Panc320 demonstrated a more pronounced anti-proliferative effect in the combination of ETC-159 and paclitaxel but not with gemcitabine. Panc269 and Panc320 were implanted into nude mice and treated with ETC-159, paclitaxel, and gemcitabine as single agents and in combination. The combination of ETC-159 and paclitaxel demonstrated an anti-tumor effect greater than ETC-159 alone but the growth inhibition was driven by paclitaxel alone. Similar results were observed in the Panc320 xenograft. At the end of treatment, drug was removed and regrowth is being monitored.

Conclusion: Based on the results obtained, each pancreatic organoid demonstrated different niche factor dependencies providing an avenue for targeted therapy, particularly with Wnt inhibition, which was supported through growth analysis following combinatory treatment of Wnt inhibitor and standard chemotherapy in vitro. The clinical utilization of this combinatory treatment modality in pancreatic cancer PDOs has thus far been supported in our patient-derived xenograft models treated with Wnt inhibitor plus paclitaxel or gemcitabine. WES and gene expression analysis of each organoid will be done as an additional avenue of analysis to comprehensively correlate genotype and Wnt (in)dependency observed in vitro.

42. INCIDENCE OF AND RISK FACTORS FOR CHYLE LEAK AFTER PANCREATIC RESECTION: A NATIONWIDE ANALYSIS

S Augustinus, AEJ Latenstein, BA Bonsing, ORC Busch, B Groot Koerkamp, IHJT de Hingh, VE de Meijer, IQ Molenaar, HC van Santvoort, J de Vos-Geelen, CH van Eijck, MG Besselink
Presenter: Simone Augustinus MD, PhD | Academic Medical Center, Netherlands

Background: In 2017, the International Study Group for Pancreatic Surgery (ISGPS) published a consensus definition of chyle leak (CL). Multicenter series assessing the ISGPS-CL definition are lacking and previous studies investigating risk factors for CL have used different definitions and showed heterogeneous results. The aim of this study was to assess the clinical impact of the ISGPS-CL definition and investigate risk factors associated with CL.

Methods: Observational cohort study including patients who underwent pancreatoduodenectomy in the mandatory nationwide Dutch Pancreatic Cancer Audit (2017-2019). Only clinically relevant CL (grade B/C) was included. Prolonged length of stay was defined as more than 14 days. Multivariable logistic regression models were performed.

Results: Overall, 2159 patients after pancreatoduodenectomy were included. The rate of CL was 7.0% (n=152), including 6.9% (n=150) grade B and 0.1% (n=2) grade C. After adjustment for confounders, CL was associated with a prolonged hospital stay (OR 2.84, 95% CI 1.85-4.36, $p < 0.001$). CL was not associated with in-hospital mortality. Vascular resection, i.e. arterial and/or venous resections (OR 2.1, 95% CI 1.4-3.2, $p < 0.001$) and open surgery (OR 3.5, 95% CI 1.7-7.2, $p = 0.001$) were identified as independent predictors for CL in multivariable analyses, whereas the number of lymph nodes resected was not.

Conclusion: The incidence of ISGPS-CL was 7.0% in a nationwide audit, with CL grade C being extremely rare (0.1%). CL was not associated with mortality, but hospital stay was longer. Vascular resection and open surgery were independent predictors for CL.

43. IS PREOPERATIVE BILIARY STENTING ASSOCIATED WITH RATES OF POSTOPERATIVE COMPLICATIONS FOR PATIENTS UNDERGOING PANCREATODUODENECTOMY? A REVIEW OF NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM DATA

EJ Olecki, R Perez-Holguin, K Stahl, W Wong, J Peng, MEB Dixon
Presenter: Elizabeth Olecki MD | Penn State Milton S. Hershey Medical Center, United States

Background: Biliary obstruction with associated jaundice is a common presentation of neoplasms in the head of the pancreas and is often treated with endoscopic biliary stent placement to allow for drainage prior to surgical resection, especially when pursuing neoadjuvant treatment. As utilization of neoadjuvant treatment continues to rise, use of preoperative biliary stenting will also likely continue to increase in this population. A prior randomized trial demonstrated trend towards increased surgical complications with preoperative biliary stenting. Despite increasing frequency of use, the relationship of endoscopic biliary stenting and postoperative complications has not been well described using multi-institutional data.

Methods: Data from the National Surgical Quality Improvement Project (NSQIP) Pancreatectomy Targeted Participant Use Data File (PUF) was used to identify all patients from 2014-2017 who underwent pancreatoduodenectomy for malignant neoplasms. Those who had endoscopic biliary stent and those without preoperative biliary stent were included in the study. Patients with percutaneous stents were excluded. Chi-square test and multivariable logistic regression were used to compare demographic, oncologic, and short-term outcomes between groups with and without preoperative biliary stent placement.

Results: Of the 5,524 patients included in this study, 3,321 (60.1%) had endoscopic biliary stents placed prior to surgical resection. The stent group was older, more likely to be male, had a higher ASA class, had significant preoperative weight loss, and had a higher rate of neoadjuvant chemotherapy and radiation compared to the group without preoperative biliary stenting (all $p<0.05$). Prior to surgery, average serum total bilirubin was higher in the stent group (2.0 mg/dl) compared to the non stent group (1.5 mg/dl) ($p<0.001$).

The stent group had longer median operative time compared to the non-stent group (364 minutes vs 352 minutes, $p=0.003$), greater percentage with hard gland texture (49.1% vs 36.4%, $p<.001$), and were more likely to have vascular reconstruction at the time of surgery (16% vs 13.7%, $p=0.02$). When controlling for demographic and operative characteristics, the non-stent group had lower overall complications rates and lower rates of post-operative infections compared to the stent group. There was no significant difference in mortality and rate of pancreatic fistula when comparing the groups (see attached table).

Conclusion: Preoperative endoscopic biliary stenting is commonly performed prior to pancreatoduodenectomy, with 60.1% of patients in this study found to have preoperative biliary stent placement. In this analysis, preoperative stenting was not associated with increased postoperative mortality or rate of pancreatic fistula, however, stent placement was associated with higher rates of overall postoperative complications, specifically infectious complications. Recognition of increased rates of overall complications associated with stent placement allows for a more accurate risk-benefit analysis when developing perioperative surgical planning for patients undergoing pancreaticoduodenectomy for malignant pancreatic head neoplasms. Despite the increased use of neoadjuvant therapy, upfront surgery for appropriate candidates should be considered.

Outcome:		OR	L 95% CI	H 95% CI	p-value
1 or more Post-Operative Complication	Endoscopically Placed Stent	**Reference**			
	No Stent	0.85	0.75	0.95	0.01
Postoperative Infection*	Endoscopically Placed Stent	**Reference**			
	No Stent	0.58	0.49	0.68	<.001
Pancreatic Fistula	Endoscopically Placed Stent	**Reference**			
	No Stent	1.02	0.85	1.21	0.87
Mortality					
	Endoscopically Placed Stent	**Reference**			
	No Stent	0.61	0.37	1.03	0.06

Multivariable logistic regression predicting outcome of 1 or more postoperative complication, infection, pancreatic fistula, and mortality while adjusting for age, sex, race, gland texture, duct size, diagnosis, and vascular reconstruction.

*includes superficial surgical site infection, deep surgical site infection, and postoperative sepsis.

44. PREVALENCE AND RISK FACTORS FOR PANCREATIC INSUFFICIENCY AFTER PANCREATECTOMY

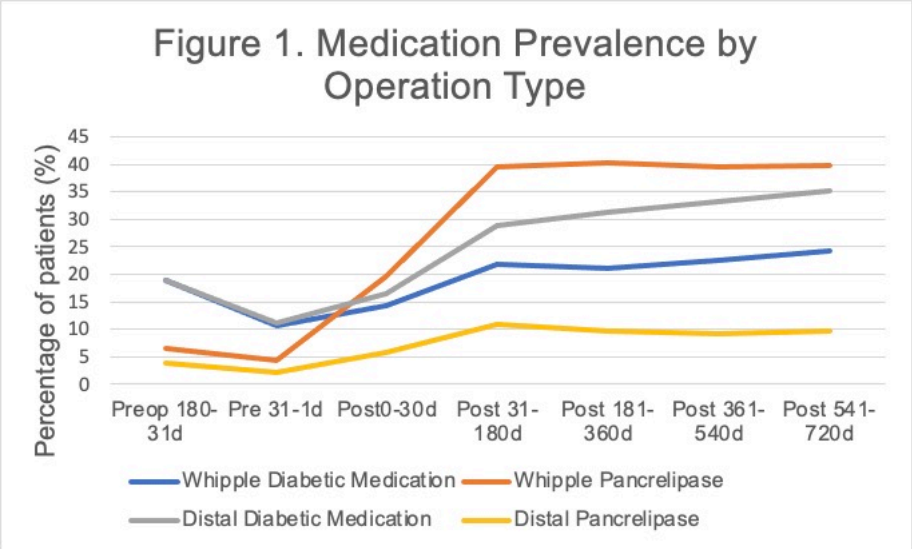
A Thomas, W Kwon, Y Huang, B Schrope, K Sugahara, J Chabot, J Wright, M Kluger
Presenter: Alexander Thomas MD | Columbia University, United States

Background: The incidence, timing, and predictors of endocrine and exocrine insufficiency after partial pancreatectomy are not well established. This study investigated medication prescription patterns in a national sample. It aimed to elucidate details to improve individualized counseling and inform studies targeting interventions for patients most at risk for these outcomes and their potential impact on QoL.

Methods: A retrospective study using IBM Watson Health MarketScan examined pancreatic replacement prescription fulfillment patterns pre- and post-pancreatectomy between 2008-2016. Multivariable models explored associations between clinical characteristics and medication use.

Results: In total, 18.96% of 2,848 pancreaticoduodenectomy (PD) patients and 18.95% of 1,858 distal pancreatectomy (DP) patients used diabetic medications preoperatively. Fewer (6.6% and 3.88%, respectively) used pancreatic enzyme replacement therapy (PERT). Total prevalence of diabetic medication increased postoperatively to 28.69% for PD and 38.59% for DP (p40, Elixhauser comorbidity index >2, and obesity. Incidence of new diabetic medication use among medication naïve patients was 13.78% for PD and 24.7% for DP at median 4.7 and 4.9 months post-operatively. Of those on oral medications preoperatively, 78.97% progressed to insulin within 1-24 months after surgery. Postoperative prevalence of PERT use was 55.97% (PD) and 17.06% (DP), p<0.0001. Compared to patients after PD, DP patients had a lower adjusted relative risk of PERT use [0.37 (0.33, 0.41), p<0.0001]. Incidence of postoperative PERT use in medication naïve patients was 53.98% (PD) and 14.84% (DP), p<0.0001. Median time to new PERT use was 3.0 (PD) and 3.2 (DP) months post-operatively. Prevalence of diabetic medication and PERT use was also evaluated across time, with use rising sharply and plateauing at 31-180 days after surgery.

Conclusion: PD was more likely to result in PERT use while DP was more likely to result in diabetic medication use. Prevalence for both peaked and plateaued in the first six months after surgery. This study provides key information to improve the understanding of predictive factors for the development of postoperative pancreatic insufficiency and the timing of disease onset. Its findings are applicable to preoperative counseling, risk modification strategies and ongoing work on pancreatectomy-related quality of life.



45. DOES NEGATIVE PRESSURE WOUND THERAPY REDUCE SUPERFICIAL AND DEEP SURGICAL SITE INFECTIONS AFTER PANCREATIC SURGERY?

EM Gleeson, RM Platoff, CH Davis, HA Pitt
Presenter: Elizabeth Gleeson MD, MPH | Mount Sinai Hospital, United States

Background: The role of negative pressure wound therapy (NPWT) in the prevention of superficial and deep surgical site infections (SSIs) after pancreatic surgery remains controversial. Randomized and retrospective trials of NPWT have demonstrated mixed results. Small numbers of patients and inadequate control for wound protectors and antibiotic prophylaxis have been confounding issues. This analysis aims to determine the role of NPWT in a large cohort of patients undergoing pancreatic surgery controlling for numerous patient, perioperative, and operative factors.

Methods: The 2019 ACS-NSQIP procedure-targeted pancreatectomy dataset was utilized. Patients undergoing open pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy were included. Multiple variables known to be associated with SSIs including wound protectors and prophylactic antibiotic type were studied. Antibiotics were dichotomized as broad spectrum or not (primarily various generations of cephalosporins). Univariable and multivariable analyses as well as propensity score matching were employed.

Results: Of 6,779 patients, 521 (7.8%) were managed postoperatively with NPWT. Broad spectrum antibiotics were given prophylactically to 35%, and wound protectors were used in 26% of patients. NPWT was applied more frequently in non-smokers and in patients who had ASA≥3, preoperative jaundice, biliary stents, neoadjuvant therapy, Whipple procedures, and less frequently in those with intraoperative drains placed. On univariable analysis, NPWT was not associated with fewer superficial/deep SSIs. These observations were confirmed by multivariable analyses (Table) and propensity score matching.

Conclusion: NPWT does not prevent superficial and deep SSIs after pancreatic surgery. Broad spectrum antibiotics are associated with fewer superficial wound infections and should be utilized more often.

Table. Multivariable analysis of characteristics associated with superficial/deep SSIs

Characteristic	OR (95% CI)	p-value
Whipple Procedure	1.86 (1.35-2.58)	<0.001
Preop Biliary Stenting	1.80 (1.39-2.32)	<0.001
Smoker within a year	1.33 (1.02-1.72)	0.033
NPWT	1.12 (0.80-1.59)	0.512
Wound Protector	0.83 (0.65-1.06)	0.126
Broad Spectrum Antibiotics	0.68 (0.55-0.86)	<0.001

46. THE IMPORTANCE OF SURGEON EXPERIENCE IN PANCREATODUODENECTOMIES AT HIGH RISK FOR FISTULA DEVELOPMENT

F Casciani, MT Trudeau, HJ Asbun, CG Ball, C Bassi, S Behrman, AC Berger, MP Bloomston, MP Callery, JD Christein, M Falconi, C Fernandez-del Castillo, ME Dillhoff, EJ Dickson, E Dixon, WE Fisher, MG House, SJ Hughes, TS Kent, G Malleo, S Partelli, RR Sale

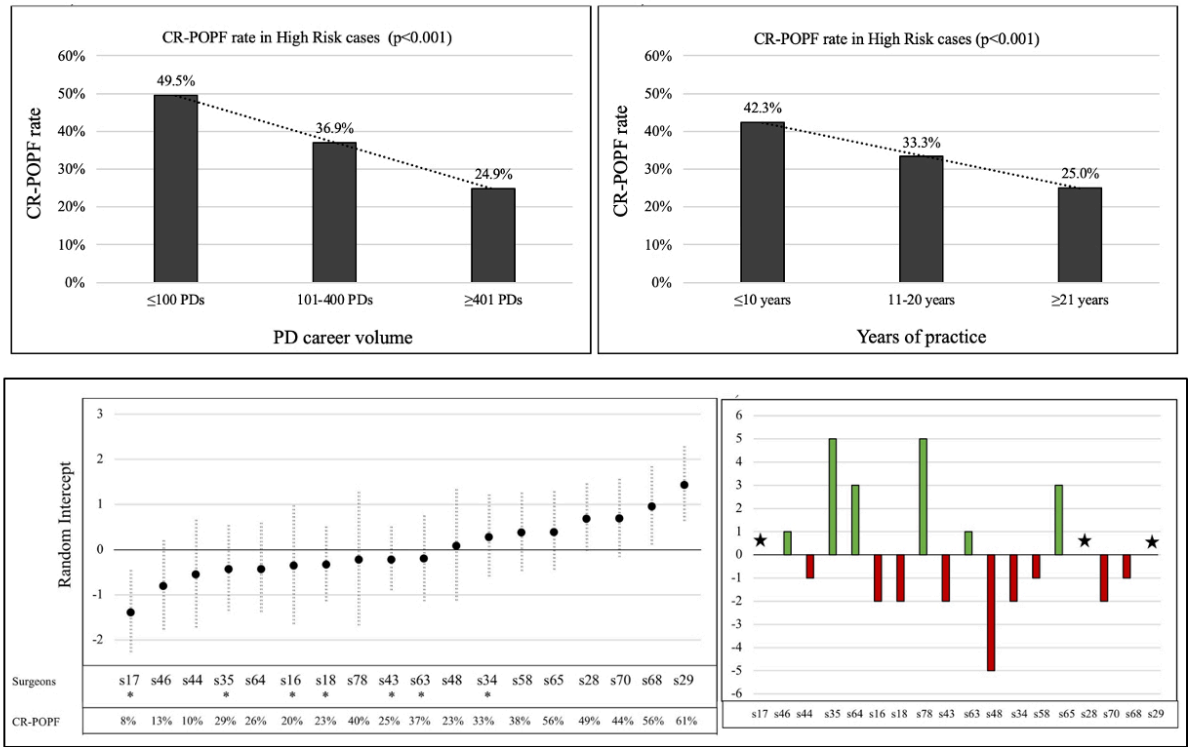
Presenter: Fabio Casciani MD | University of Pennsylvania, United States

Background: Despite a hospital volume-outcome relationship being recognized in pancreatic surgery, pancreatoduodenectomies (PDs) at high risk for clinically-relevant pancreatic fistula (CR-POPF) development are intimidating situations even at high volume institutions. In such scenarios, the impact of individual surgeon experience on outcomes is poorly understood.

Methods: From 7706 PDs performed at 18 institutions (2003-2020), the Fistula Risk Score (FRS) was employed to identify 830 High Risk patients (FRS 7-10) operated on by 64 surgeons. For each case, surgeon PD career volume and years of practice were linked to intraoperative fistula mitigation strategy adoption and outcomes. Best performers for CR-POPF occurrence were identified through a generalized linear mixed model (hierarchical clustering) accounting for both case-mix and intraoperative factors, while best operative approaches for CR-POPF prevention were defined through logistic regression models.

Results: Despite a significant variability being observed across institutions (range: 2.7-32.2%) and individual surgeons (0.0-39.0%; both p<0.001), the incidence of High Risk operations did not change across surgeon experience classes. Contrarily, CR-POPF rates decreased with escalating surgeon career PD volume (-49.7%) and career length (-41.2%; both p<0.001; Figure, top), as did operative time, transfusion, reoperation rates, Postoperative Morbidity Index, length-of-stay and mortality. On MVA, great surgeon experience (≥400PDs performed or ≥21year-long career) was an independent predictor of CR-POPF prevention (OR 0.52, 95%CI 0.35-0.76; p<0.001), whereas pancreatico-gastrostomy (OR 1.93) and prophylactic Octreotide (OR 2.39) were contributors to CR-POPF. The risk-adjusted surgeon performance analysis also correlated with experience, with best and worse performers being senior and junior surgeons respectively (Figure, bottom). Concerning individual behaviors, surgeons who had a constant approach (namely, applied the same pattern of intraoperative mitigation strategies on more than 90% of occasions) had significantly lower CR-POPF rates compared to their peers (19.4 vs 36.8%; p<0.001), with greater experienced surgeons employing less patterns (median: 2 vs 4; p<0.001). Approaches including pancreaticojejunostomy reconstruction and prophylactic Octreotide omission, with or without trans-anastomotic stent or drains, were associated with reduced CR-POPF rates among both less (32.4 vs 49.3%) and greater experienced surgeons (20.3 vs 43.0%; both p<0.001), but were employed more consistently by the latter (75.5 vs 52.8%; p<0.001). Moreover, minimizing blood loss (≤400mL) significantly contributed to CR-POPF prevention (OR 0.40, 95%CI 0.22-0.74), irrespective of surgeon experience and the pattern of mitigation strategies employed.

Conclusion: When compared to younger peers, expert surgeons display improved outcomes, a more standardized practice, and a more consistent employment of strategies independently associated with lower fistula rates following High Risk pancreatoduodenectomies. Therefore, this data advocate for intraoperative consultation and tutoring by expert surgeons when facing such high stake situations. However, all surgeons can improve their performance by employing pancreatojejunostomy reconstruction, omitting prophylactic Octreotide and minimizing blood loss.



Top. Relationships between surgeon experience [as either personal PD career volume (left panel) or years of practice (right panel)] with CR-POPF rates in 830 High Risk cases derived from 7706 pancreatoduodenectomies from the Pancreas Fistula Study Group. **Bottom.** Left panel: caterpillar plot indicating risk-adjusted ranking for CR-POPF occurrence across surgeons who have performed ≥15 High Risk FRS pancreatoduodenectomies. Greater Experienced surgeons (>400 PDs and/or ≥21 years practice) are starred. Right panel: differences between overall CR-POPF rate and risk-adjusted (intercept) ranks. Six surgeons improved their rank when considering the risk adjusted analysis with respect of their overall CR-POPF rates (positive values, in green), while nine surgeons slipped down in the ranking (negative values, in red). Stars indicate surgeons with no difference between overall and risk-adjusted rank.

47. POST-PANCREATECTOMY VOLUMETRIC ANALYSIS: A MISSING VARIABLE IN THE DEVELOPMENT OF POST-OPERATIVE ENDOCRINE AND EXOCRINE DYSFUNCTION

ME Johnston, SA Wahab, KM Turner, DJ Hanseman, SA Ahmad,, SH Patel, GC Wilson
Presenter: Michael Johnston MD | University of Cincinnati, United States

Background: Postoperative pancreatic endocrine (PEnDef) and exocrine deficiency (PExDef) are a source of long-term morbidity after pancreatic resection. Most previous reports have focused on patient characteristics without including volumetric analysis. The aim of this current study is to evaluate factors associated with postoperative PEnDef and PExDef including volumetric analysis.

Methods: Consecutive patients undergoing formal pancreatic resection between 2017-18 at a single institution were examined. Patients with a minimum of 1 year follow up with complete postoperative outcomes and imaging were included. Diabetes was diagnosed according to established ADA definitions. PExDef was determined by requiring pancreatic enzyme replacement at 1-year post op. Pre- and post-operative pancreatic volumes were calculated by a single blinded radiologist with expertise in pancreatic imaging using GE AW Server 3.2 volumetric software.

Results: Sixty-eight patients underwent pancreatectomy that met inclusion criteria. 47% (n=32) of patients were female, median BMI was 27.45 kg/m2 (±5.74), 57% (n=39) were diagnosed with pancreatic adenocarcinoma, and 66% (n=45) underwent pancreaticoduodenectomy while the remainder (34%, n=23) underwent distal pancreatectomy.

The overall incidence of PEnDef was 32.5% (n=13) and PExDef was 50% (n=27). The incidence of PEnDef was higher after distal (57% vs. 16%, p 0.01) and the incidence of PExDef was higher after Whipple (66% vs 21%, p 0.004). Mean preoperative pancreas volume was 76.2 mm3 ±51.22 for all patients. the mean post pancreatectomy remnant volume after Whipple was 23.1 ±21.4 mm3 (range = 5 -65 mm3) with 67.3% volume resected, while after distal pancreatectomy the mean post pancreatectomy remnant volume was 44.8 mm3 +/- 19.5 (range = 17 to 70 mm3) with mean of 37.7% resected.

Logistic regression analysis was performed for predictors of PEnDef and PExDef as listed in Table 1. The only factors associated with PEnDef on multivariate analysis were presence of hyperlipidemia (OR=76, 95%CI 3.39-999, p value 0.01) and undergoing distal pancreatectomy (OR=30.3, 95%CI 1.58-581, p value 0.02). On multivariate analysis the only factor associated with PExDef was postoperative remnant pancreas volume (OR=0.93, 95%CI 0.88-0.98. p value < 0.01).

Conclusion: Postoperative pancreas remnant volume was the only factor associated with the development of exocrine insufficiency after pancreas resection. While patient factors such as hyperlipidemia and type of resection were associated with PEnDef. These models can be used to counsel patients on risk of post-pancreatectomy endocrine and exocrine deficiency before surgery.

Table 1: Logistic Regression Analysis PEnDef. and PExDef.

	Endocrine Deficiency				Exocrine Deficiency			
	Univariate (N=46)		Final Model (N=46)		Univariate (N=54)		Final Model (N=54)	
Predictor	**Univariate**	**p Value**	**Multivariate**	**p Value**	**Univariate**	**p Value**	**Multivariate**	**p Value**
Postop Volume	1.04 (1.00-1.09)	0.06	0.99 (0.91-1.08)	0.89	0.94 (0.90-0.98)	**<0.01**	0.93 (0.88-0.98)	**<0.01**
Pct. Volume Resected	0.49 (0.02-14.4)	0.68	-	-	266 (6.52 - 999)	**<0.01**	10.8 (0.03 – 999)	0.42
Preop HbA1c	1.69 (0.69-4.11)	0.25	-	-	1.17 (0.70-1.96)	0.55		
ADA Classification								
Normal	0.88 (0.07-10.5)	0.92	-	-	0.67 (0.17 – 2.67)	0.57	-	-
Prediabetic	2.00 (0.23-39.6)	0.4	-	-	0.67 (0.14-3.09)	0.6	-	-
Diabetic	1.00 (ref.)		-	-	1.00 (ref.)		-	-
Preoperative BMI	1.14 (0.99-1.32)	0.07	1.12 (0.87-1.45)	0.37	0.96 (0.88-1.04)	0.3	-	-
Distal Pancreatectomy	7.20 (1.73-29.9)	**<0.01**	30.3 (1.58 - 581)	**0.02**	0.14 (0.04-0.51)	**<0.01**	0.56 (0.07-4.45)	0.58
Age at Dx	1.02 (0.97-1.08)	0.4	-	-	1.04 (0.99-1.08)	0.09	-	-
Current Smoker	0.47 (0.05-4.43)	0.5	-	-	1.00 (ref.)		-	-
Prior Smoker	1.40 (0.37-5.35)	0.62	-	-	0.52 (0.07-3.70)	0.52	-	-
Hyperlipidemia	32.0 (3.62-283)	**<0.01**	76.0 (3.39 - >999)	**<0.01**	0.94 (0.31-2.80)	0.91	-	-
Adjuvant Chemo	1.60 (0.37-7.02)	0.53	-	-	3.10 (0.90-10.6)	0.07	2.08 (0.50-8.71)	0.31
Major Complication	0.82 (0.14-4.70)	0.82	-	-	1.31 (0.31-5.56)	0.72	-	-
Neoadjuvant Radiation	0.28 (0.05-1.54)	0.14	0.03 (<0.01 – 5.14)	0.17	0.50 (0.12-2.09)	0.34	-	-
Neoadjuvant Chemotherapy	0.22 (0.04-1.14)	0.07	23.0 (0.13 - >999)	0.23	1.05 (0.31-3.67)	0.93	-	-

Values with p Value <0.05 bolded.

48. A NATIONWIDE ANALYSIS OF PANCREATIC CANCER TRIAL ENROLLMENT REVEALS DISPARITIES AND PARTICIPATION PROBLEMS

JJ Hue, K Sugumar, E Katayama, JB Ammori, LD Rothermel, JM Hardacre, JM Winter, LM Ocuin
Presenter: Jonathan Hue MD | University Hospitals Cleveland Medical Center, United States

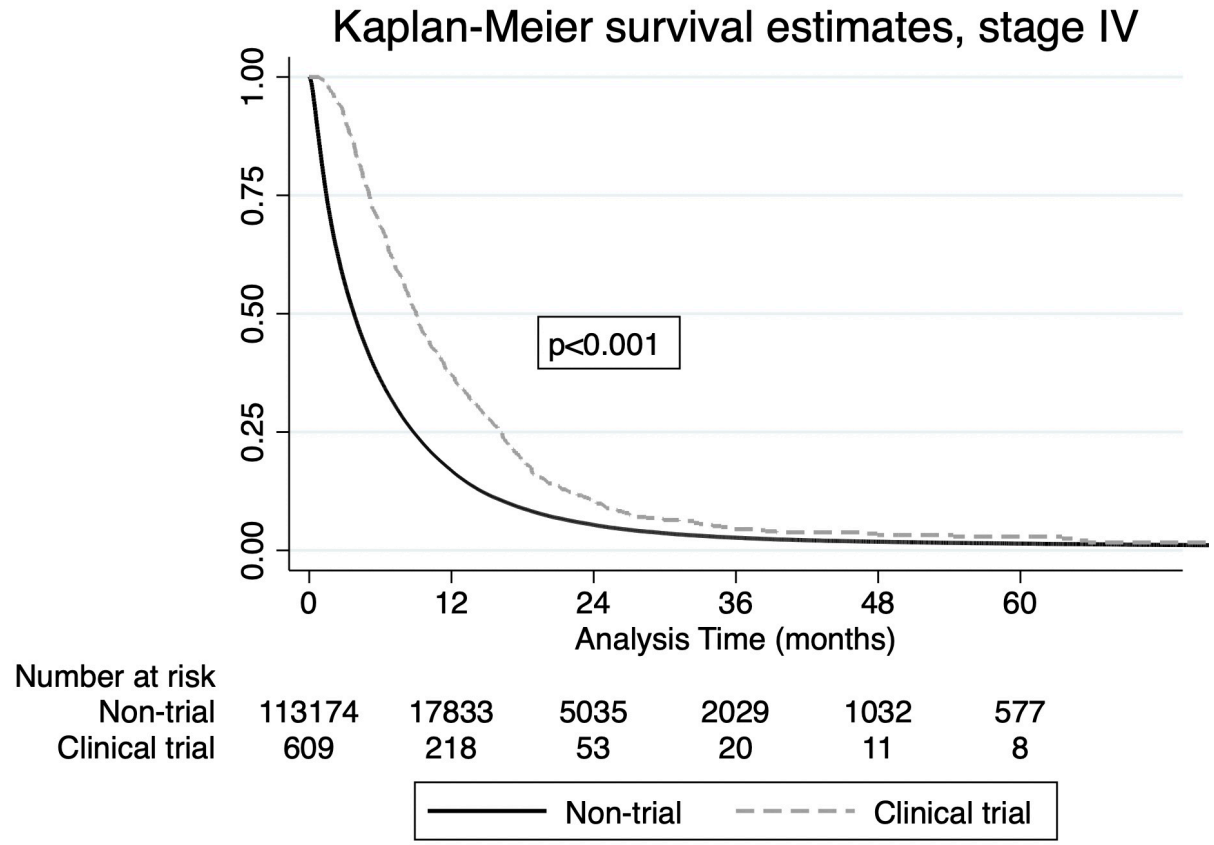
Background: Our research group recently surveyed the current clinical trial landscape in pancreatic ductal adenocarcinoma (PDAC). We identified 430 active clinical trials, of which 37 were in phase III testing. These ongoing clinical trials represent an opportunity to expand treatment options for patients with PDAC, a disease in desperate need of novel therapies. Our primary objective was to detail the rate of and factors associated with clinical trial participation among patients with PDAC using an administrative database. Our secondary objective was to evaluate survival associated with trial participation.

Methods: We queried the National Cancer Database (2004-2016) for patients with pancreatic adenocarcinoma. All stages of disease were included. Patients were divided into two treatment groups: clinical trial or non-trial. Multivariable logistic regression was used to identify variables associated with participation in a clinical trial. Additionally, marginal standardization was used to calculated odds of trial participation adjusted to the weight of potential confounders. The Kaplan-Meier method and multivariable Cox hazards regression were used to analyze overall survival. Receipt of other therapies (systemic therapies, radiotherapy, pancreatectomy) was factored into analyses.

Results: A total of 261,483 patients were included, of whom 1,110 (0.4%) were enrolled in a clinical trial. A total of 57 Black patients were enrolled in a clinical trial over the 13-year study period (0.18% of Black patients). This was significantly lower as compared to White patients (n=1,001, 0.46% of White patients, p<0.001). Among patients with stage IV disease, clinical trial participants were younger (63 vs 68 years), more likely to be White (89.7% vs 82.8%), have a greater household income and education level, have private insurance (51.7% vs 32.5%), and receive treatment at an academic facility (81.4% vs 37.9%) as compared to non-trial patients (p<0.001 for all comparisons). Similar demographic differences were present among patients with localized (stage I-III) disease. After adjusting for demographic and clinical factors, Black patients were less likely to be enrolled in a clinical trial (odds ratio=0.38, p<0.001) as compared to White patients. Patients from areas of lower education were less likely to be in a clinical trial, as were patients treated at non-academic medical centers. Using marginal standardization, White patients age 60-69 years were more likely be in a clinical trial relative to Black patients (adjusted probability: 0.006 vs 0.003).

Participation in a clinical trial was associated with an increased median survival as compared to the non-trial patients among those with stage IV disease (9.0 vs 3.8 months, p<0.001, Figure). This association remained on multivariable Cox regression (hazard ratio (HR)=0.78, p<0.001) when controlling for demographic and treatment details. A similar association with survival was seen among stage I-III patients (18.8 vs 12.1 months, p<0.001; HR=0.86, p=0.005).

Conclusion: Fewer than 1% of patients with PDAC participated in a clinical trial during the study period. There are racial and sociodemographic disparities in clinical trial enrollment, which identifies an important area for future targeted efforts in improving participation. Lastly, clinical trial participants appear to have an associated survival advantage relative to non-trial patients, further highlighting the importance of ongoing trial participation.


Kaplan-Meier survival estimates, stage IV
1.00
0.75
0.50
0.25
0.00
p<0.001
0
12
24
36
48
60
Analysis Time (months)
Number at risk
Non-trial 113174 17833 5035 2029 1032 577
Clinical trial 609 218 53 20 11 8
Non-trial
Clinical trial

49. THE IMPACT OF MOLECULAR SUBTYPING ON PATHOLOGICAL STAGING OF PANCREATIC CANCER

SB Dreyer, S Rae, K Bisset, R Upstill-Goddard, G Gemenetzis, AL Johns, Australian Pancreatic Cancer Genome Initiative, Glasgow Precision Oncology Laboratory, EJ Dickson, A Mittal, AJ Gill, F Duthie, A Pea, RT Lawlor, A Scarpa, R Salvia, A Pulvirenti, A Ze

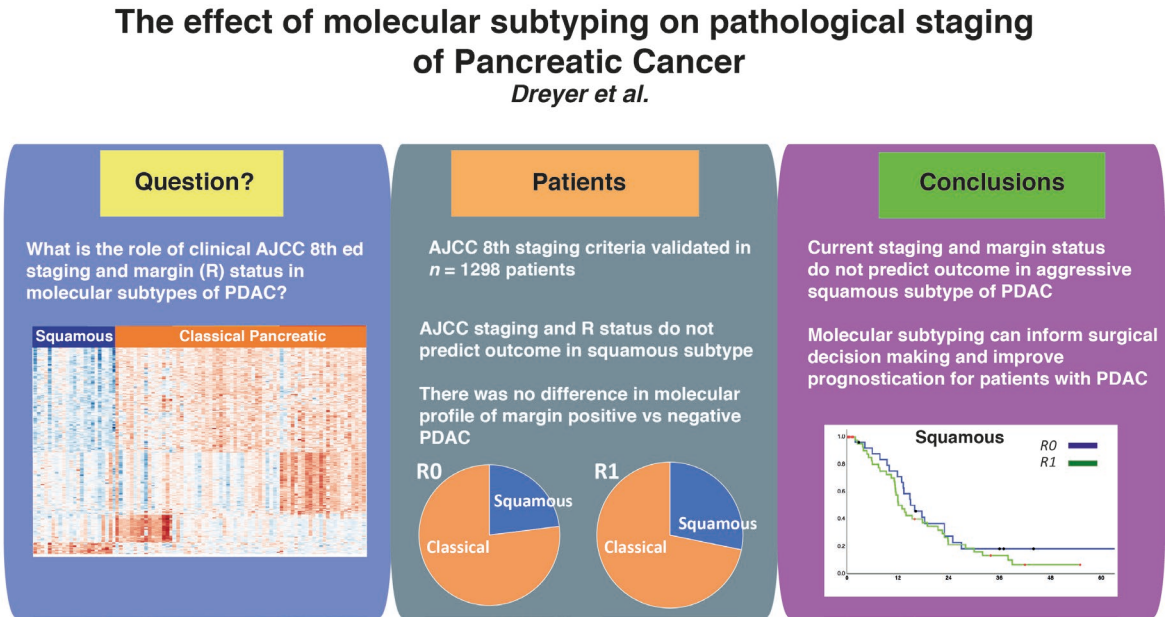
Presenter: Stephan Dreyer MD, PhD | University of Glasgow, United Kingdom

Background: The long-term outcomes following surgical resection for Pancreatic Ductal Adenocarcinoma (PDAC) remains poor, with only 20% of patients surviving 5 years after pancreatectomy. Patient selection for surgery remains sub-optimal largely due to the absence of consideration of aggressive tumor biology. The aim of this study was to evaluate traditional staging criteria for PDAC in the setting of molecular subtypes.

Methods: Clinicopathological data were obtained for 5 independent cohorts of consecutive unselected patients, totaling n = 1298, including n = 442 that underwent molecular subtyping. The main outcome measure was disease specific survival following surgical resection for PDAC stratified according to the American Joint Commission for Cancer (TNM) staging criteria, margin status and molecular subtype.

Results: TNM staging criteria and margin status confers prognostic value only in tumors with classical pancreatic subtype. Patients with tumors that are of squamous subtype, have a poor outcome irrespective of favorable traditional pathological staging (HR 1.54, 95%CI 1.04 – 2.28, P = 0.032). Margin status has no impact on survival in the squamous subtype (16.0 vs 12.1 months, P = 0.374). There were no differences in molecular subtype or gene expression of tumors with positive resection margin status.

Conclusion: Aggressive tumor biology as measured by molecular subtype predicts poor outcome following pancreatectomy for PDAC and should be utilized to inform patient selection for surgery.



50. TEN-YEAR NATIONWIDE SURVIVAL OF OPERATED IPMNS

Y Vaalavuo, M Vornanen, R Ahola, A Antila I Rinta-Kiikka, J Sand, J Laukkarinen
Presenter: Yrjö Vaalavuo MD | Tampere University Hospital, Finland

Background: Prognosis of patients with resected Intraductal papillary mucinous neoplasm (IPMN) is mostly dependent on the degree of dysplasia. Patients with low malignant potential tumour, such as low-grade (LG) Branch-duct (BD) IPMN have excellent prognosis compared to patient with invasive (INV) main duct (MD) or mixt-type (MT) IPMN which carries malignant potential close to ductal adenocarcinoma of the pancreas. Long-term data of operated IPMN is limited, especially in a nationwide setting.Our aim was to determine the nationwide characteristics and ten-year survival of operated IPMNs.

Methods: All IPMNs operated nationwide in Finland during 2000-2008 were included into the study database. Data on patient demographics was collected from the hospitals' files. Tumor histopathology and preoperative imaging were re-analyzed. Survival was updated on 28.11.2020.

Results: Between 2000-2008 2,024 pancreatic resections were made in Finland. Of those 2.024 resections, Final histology was IPMN in 88 cases. Median age was 65.5 (range 40-87) years, and 58% were female. 73% of the patients were symptomatic. Pancreaticodudenectomy was performed in 49%. Malignancy was suspected in 22% of the cases in preoperative imaging.
Final histopathology was 53% MD-IPMN, 31% MT-IPMN, and 16% BD-IPMN. Overall, 45.5% were LGD, 10.2% HGD and 44.3% INV. For MD, MT and BD-IPMN, distribution of dysplasia was LGD in 26-59-86%, HGD in 13-7-7% and INV in 62-33-7%.
Histological subtypes were 35% oncocytic, 48% Intestinal and 17% pancreatobiliary. Median survival in this was 121 (range 0-240) months.1/5/10 year survival was 88.6/63.6/50.0%. For MD, MT, BD-IPMN survival was 1-year 85.1-92.6-92.6%, 5-year 59.6-59.3-63.6% and 10-year 44.7-51.9-50.0% In subgroups divided by degree of dysplasia; LGD/HGD/INV survival percentages were 1-year 97.5-100-76.9 %, 5-year 87.5-77.8-35.9 %, and 10-year 72.5-72.5-23.1%.

Conclusion: IPMN resection should be timed before malignant transformation. In this nationwide study, 44% of the operated IPMNs during 2000-2008 were malignant. 10-year survival was 23% in patients with a malignant IPMN, 67% in patients with HGD and 73% in LGD. Level of dysplasia in operated IPMN is the most important long-term prognostic factor and emphasizes the timing of surgery.

51. THE USE OF ANGIOTENSIN SYSTEM INHIBITOR IN SURVIVAL OF RESECTED PDAC PATIENTS

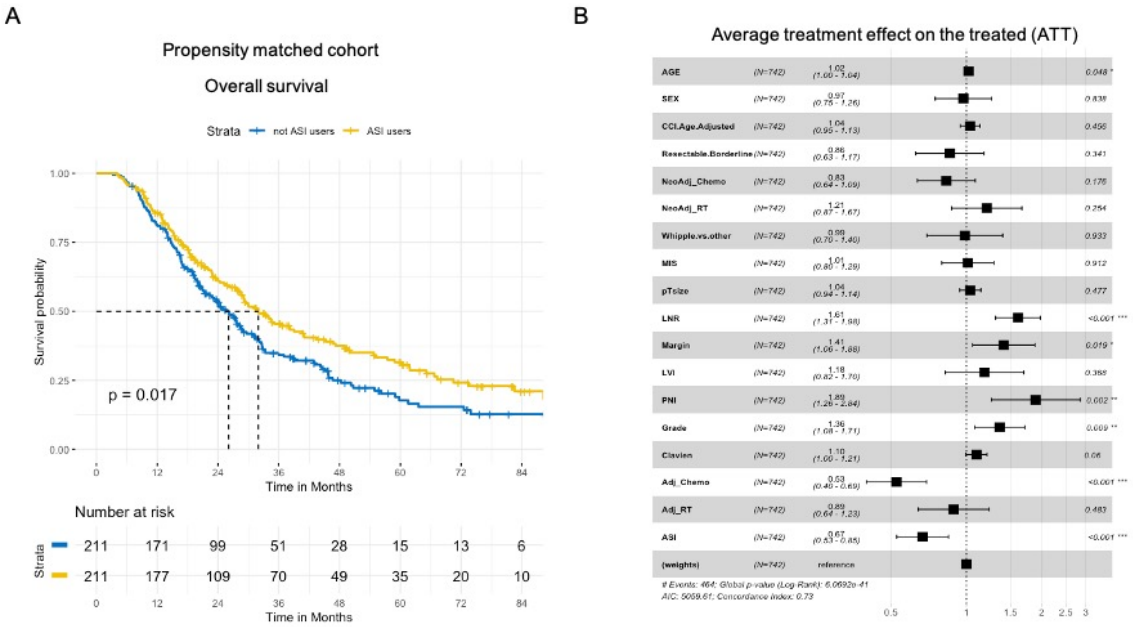
H Liu, I Nassour, M D'Alesio, S Lebowitz, A Hamad, A Desilva, S Aatur, B Nathan, K Lee, A Zureikat, A Paniccia
Presenter: Hao Liu MD PhD | University of Pittsburgh Medical Center, United States

Background: Renin angiotensin system (RAS) has crucial implications in pancreatic adenocarcinoma (PDAC) tumorigenesis and progression. Activities and inhibition of RAS may affect treatment response and may associate with clinical outcomes. Previous observational studies suggested that angiotensin system inhibitor (ASI) use is associated with better survival in a subset of patients. Our present retrospective study focused on resected PDAC patients and explored the protective effect of ASI.

Methods: This is a single institution retrospective analysis of resected PDAC patients between 2010-2019. Clinicopathological characteristics of all cases meeting inclusion criteria are reviewed. To estimate the effect of ASI on patient survivals, we performed Kaplan Meier analysis, Cox Proportional Hazards model, Propensity Score Matching (PSM), and inverse propensity score weight (IPW) analysis. Propensity score of ASI treatment is calculated by comorbidities and their treatments received.

Results: 742 patients were included in the analysis. The average age is 67.0 years old with a median follow up 24.1 months. ASI users are older (68.9 vs 65.3, $p<0.001$) and with more comorbidities. Multivariate adjustment included age, gender, age adjusted Charlson comorbidity index, resectability, neoadjuvant chemotherapy, neoadjuvant chemoradiation, surgery performed and its approach, tumor size, lymph node ratio, margin status, invasion, grade, post-operative complication, adjuvant chemotherapy and adjuvant chemoradiation. We also adjusted for history of coronary artery disease, diabetes, hyperlipidemia and hypertension, as well as the use of beta blockers, diuretics, metformin and statins. The use of ASI is significantly associated with longer overall survival in univariate (HR = 0.76 [0.67-0.86], $p=0.004$) and multivariate(HR = 0.71 [0.57-0.89], $p=0.003$) adjusted analysis. In propensity score matched cohort 422 patients, ASI use again associated with longer overall survival (HR = 0.74 [0.58-0.94], $p=0.014$) as well as longer disease progression in the liver, lung and but not local recurrence. Lastly, using inverse probability weighting (IPW) analysis on the whole cohort of 742 patients showed that the use of ASI is associated with an average treatment effect on the treated (ATT) of HR = 0.67 [0.53-0.85] ($p<0.001$) for overall survival.

Conclusion: In this single institute retrospective study focusing on resected PDAC patients, the use of ASI is associated with longer overall survival, after adjusting for multiple clinicopathological parameters. Propensity score matching and IPW analysis also showed that ASI use is associated with longer overall free survival. Further prospective trial on resectable PDAC is needed.



Abstract Figure: A) Kaplan-Meier analysis on PDAC patients' overall survival with or without ASI use in propensity score-matched cohort of 637 patients. The propensity score is calculated by the comorbidity parameters of coronary artery disease, diabetes, hyperlipidemia, hypertension, and the use of beta-blockers, diuretics, metformin, and statins. The use of ASI is significantly associated with longer overall survival in univariate analysis. ASI use defined when patients are taking ASI at diagnosis and for >28d of the follow up time. B) Cox proportional hazard model for the average treatment effect on the treated (ATT) estimation on the whole cohort with inverse propensity weighted analysis. The propensity score is calculated with the comorbidity parameters of coronary artery disease, diabetes, hyperlipidemia, hypertension, and the use of beta-blockers, diuretics, metformin, and statins. ASI is associated with significantly protective ATT and ATE (not shown) on PDAC overall survival. *CCI_age_adjusted: age adjusted Charles-comorbidity index; NeoAdj_Chemo: neoadjuvant chemotherapy, MIS: minimally invasive surgery (laparoscopic or robotic assisted pancretectomies), LNR: lymph node ratio; LVI: lymphovascular invasion; PNI: perineural invasion; ASI: angiotensin system inhibitor use.*

52. FEATURES OF T1 PANCREATIC CANCER AND VALIDATION OF ITS DEFINITION BY THE EIGHTH EDITION AJCC STAGING SYSTEM USING A KOREAN JAPANESE JOINT COHORT AND THE SEER DATABASE

W Kwon, JY Jang, H Kim, CS Lim, YS Yoon, JS Park, I Endo, Y Nagakawa, M Kawai, H Yamaue
Presenter: Wooil Kwon MD, PhD | Seoul National University College of Medicine, Korea

Background: The definition of T1 pancreatic cancer was modified by the eighth edition of the American Joint Committee on Cancer staging system. Major changes of T1 pancreatic cancer definition were the newly introduced T1 subcategorization and the removal of extrapancreatic extension concept. The new definition increases the prevalence of T1 pancreatic cancer. However, T1 pancreatic cancers by itself is less studied owing to its relative rarity. In addition, the validity of these changes has never been investigated. The aim was to study the clinicopathologic features of T1 pancreatic cancer and to investigate the validity of its definition and subcategorization.

Methods: Patients who was confirmed to have T1 pancreatic ductal adenocarcinoma (PDAC) after resection between 2000 and 2019 was identified from 42 high-volume centers in Korea and Japan and was retrospectively reviewed. Patients with adenocarcinoma arising from premalignant lesions or pancreatic cancer of other subtypes than adenocarcinoma were excluded. Patients who received neoadjuvant treatment, did not have lymph node evaluation, or had distant metastasis at operation were also excluded. Survival analyses and multivariate analyses were done. Patients who were operated and confirmed to have PDAC of 2 cm or less without distant metastasis between 2000 and 2016 were queried from the Surveillance, Epidemiology, and End Result (SEER) database. Using the SEER database, the results from the Korean Japanese cohorts were validated.

Results: Data of 1,459 patients with T1 PDAC were collected. The median survival duration of T1 PDAC was 49 months, and the 5-year survival rate was 44.4%. R0 resection was unachievable in 10.3%, nodal metastasis rate was 39.8%, and recurrence occurred in 55.4%. The current T1 subcategorization was not feasible for PDAC especially between T1a and T1b. On the other hand, subdividing into 2 groups with 1.1 cm reference was feasible. Tumors with extrapancreatic extension which constituted 73.7% had worse outcome than those without (median survival 104 vs 39 months, $p<0.001$). In multivariate analysis, R status, extrapancreatic extension, N category, and adjuvant treatment were independent prognostic factors; but the current T1 subcategorization was not. A new subcategorization using size of 1.1 cm and extrapancreatic extension was able to subcategorize T1 PDACs into distinct prognostic group between all groups and also demonstrated significance in multivariate analysis (Table 1). Those who received adjuvant treatment had better survival compared to those who did not (median survival: 54 vs. 41 months, $p=0.005$). Patients with neither extrapancreatic extension nor LN metastasis were the only subgroup that did not benefit from adjuvant treatment. The results from this cohort was reproducible from the data of 3,092 T1 PDAC cases retrieved from the SEER database.

Conclusion: Despite the small size, T1 PDAC displayed an aggressive behavior warranting active local and systemic treatment. The subcategorization was not feasible for PDAC and better ways of subcategorizing need to be explored. In addition, extrapancreatic extension demonstrated a prognostic significance and its role in staging system should be reconsidered.

Table 1. Univariate and multivariate analysis for prognostic factors of T1 pancreatic cancer

Variable	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
<60 years						
≥60 years	1.120	0.945-1.328	0.190			
Sex						
Male						
Female	0.840	0.724-0.974	0.020	0.849	0.731-0.985	0.031
Location						
Head			0.089			0.570
Body	0.821	0.688-0.980	0.029	0.898	0.750-1.076	0.244
Tail	0.805	0.614-1.056	0.117	0.909	0.690-1.197	0.496
Diffuse	1.206	0.451-3.227	0.709	1.352	0.496-3.687	0.555
R status						
R0			<0.001			<0.001
R1	2.021	1.621-2.519	<0.001	1.692	1.352-2.117	<0.001
R2	5.116	2.539-10.310	<0.001	3.241	1.585-6.627	0.001
Extrapancreatic extension						
No						
Yes	1.799	1.491-2.171	<0.001	1.382	1.123-1.702	0.002
T1 subcategory						
T1a			0.008			0.266
T1b	1.033	0.480-2.223	0.933	0.872	0.402-1.890	0.728
T1c	1.839	0.985-3.434	0.056	1.253	0.655-2.396	0.496
N category						
N0			<0.001			<0.001
N1	1.660	1.415-1.946	<0.001	1.494	1.258-1.773	<0.001
N2	3.003	2.374-3.799	<0.001	2.640	2.050-3.399	<0.001
Lymphovascular invasion						
Yes			<0.001			0.404
No	0.717	0.606-0.848	<0.001	0.950	0.792-1.140	0.583
Unknown	0.992	0.812-1.211	0.935	1.116	0.899-1.387	0.320
Perineural invasion						
Yes			0.001			0.089
No	0.734	0.625-0.863	<0.001	0.885	0.744-1.053	0.168
Unknown	0.732	0.504-1.129	0.171	0.660	0.431-1.011	0.056
Adjuvant treatment						
Yes			0.001			<0.001
No	1.246	1.069-1.454	0.005	1.486	1.267-1.743	<0.001
Unknown	3.043	1.260-7.351	0.013	1.994	0.817-4.868	0.130

HR, hazard ratio; CI, confidence interval.

53. DYNAMIC SURVIVAL ANALYSIS USING EMPIRICAL INFORMATION FOLLOWING PANCREATECTOMY FOR PANCREATIC DUCTAL ADENOCARCINOMA

L Maggino, G Lionetto, A Patton, A Esposito, L Landoni, L Casetti, M Tuveri, S Paiella, G Marchegiani, C Bassi, G Malleo, R Salvia

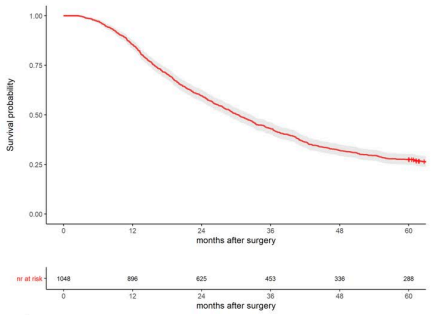
Presenter: Laura Maggino MD | University of Verona, Italy

Background: Oncologic outcomes following pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) are estimated from survival projections, which can be biased by right-censoring. Moreover, prognostic assumptions are extrapolated from static models derived at the time of surgery, with little dynamic information available thus far. The aim of this study were: i) to describe the empirical survival distribution and the characteristics of long-survivors in a cohort without censoring before 5-years post-pancreatectomy; ii) to investigate changings in the impact of baseline prognostic factors on survival and recurrence; iii) to estimate the role of unobserved heterogeneity, which is a random effect of unknown covariates on lifetimes.

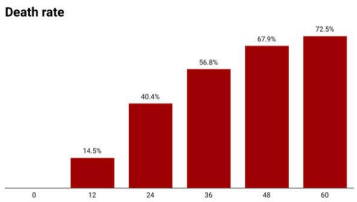
Methods: All curative-intent pancreatectomies for PDAC (2000-2015) at an academic institution were enrolled (minimum follow-up for survivors ≥60 months). The characteristics of long-survivors (≥5 years) were analyzed using multivariable logistic regression. Dynamic changings in prognostic factors over time were evaluated using a landmarking approach, whereby separate multivariable Cox-regression models were fitted at various landmark-time (1-2-3-4-5 years postoperatively), each including only patients still alive at that given landmark. Finally, to account for unmeasured heterogeneity, a frailty model was designed under the premise that each patient has an individual risk parameter (the frailty) resulting from unmeasured covariates, and that frailer patients tend to die earlier than patients who are less frail.

Results: The median follow-up of the 1048 included patients was 30.4 months, 97.2 months in survivors. The median survival was 30.4 months, with empirical 1-2-3-4-5-year rates of 85.5%, 59.6%, 43.2%, 32.1% and 27.5%. The risk function, expressing the instantaneous risk of death, showed a rapid increase within the first two years postoperatively and then progressively decreased (Figure). The median recurrence-free survival was 17.2 months (recurrence rate=73.7%). Overall, 288 patients were long-survivors. A favorable pathological profile (encompassing R0, T0-1, N0, G1, no extrapancreatic invasion) and the receipt of adjuvant treatment were independent predictors of long-survival. Nonetheless, 25.7% of long-survivors were R1, 28.8% N2. Landmark analysis showed that factors independently associated with survival and recurrence at the time of pancreatectomy, including resection margins, staging parameters, grading, and adjuvant treatment, remained robust up to two years postoperatively and relaxed subsequently. This suggests the presence of selective pressure on the study population possibly driven by unmeasured covariates. To explore this, a frailty model was introduced. This confirmed a significant unobserved heterogeneity impacting survival and recurrence in the early postoperative period and subsiding after two years postoperatively.

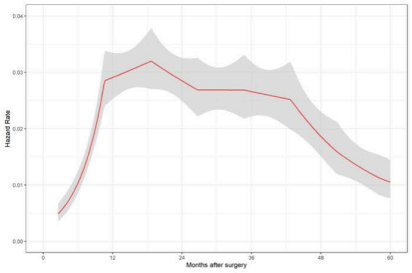
Conclusion: This study offers empirical survival information up to 5 years post-pancreatectomy. Long-survival is achieved by 27.5% of the patients undergoing resection for PDAC and is not entirely precluded by an unfavorable pathological profile. The impact of prognostic factors identified at the time of surgery tends to relax over time. There is a significant frailty effect that impacts survival and recurrence of patients, particularly in the first two years postoperatively. This unmeasured heterogeneity is likely attributable to the biological characteristics of the tumor and its interaction with the host. These results offer a framework for dynamic survival predictions, also accounting for individual heterogeneity attributable to unobserved tumor characteristics.


Survival probability
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
months after surgery
nr at risk
1048
896
625
453
336
288
0
12
24
36
48
60
months after surgery

A


Death rate
14.5%
40.4%
56.8%
67.9%
72.5%
0
12
24
36
48
60

B


Hazard Rate
0.04
0.03
0.02
0.01
0.00
0
12
24
36
48
60
Months after surgery

C

54. IS THERE A BENEFIT TO ADJUVANT CHEMOTHERAPY IN RESECTED, EARLY-STAGE PANCREATIC DUCTAL ADENOCARCINOMA?

K Turner, A Delman, E Schepers, D Sohal, O Olowokure, K Choe, M Smith, J Kharofa, S Ahmad, G Wilson, S Patel

Presenter: Kevin Turner MD | University of Cincinnati, United States

Background: Systemic therapy has an important role in the treatment of pancreatic ductal adenocarcinoma (PDAC); however, data in early-stage IA is unclear. Stage IA disease is underrepresented or completely excluded from prospective clinical trials, likely due to the infrequent nature of early-stage disease at presentation and relatively good outcomes in this subgroup. The aim of our study was to evaluate the effectiveness of adjuvant chemotherapy (AC) in resected, Stage IA disease.

Methods: The National Cancer Database (NCDB) was queried from 2004 to 2017 for resected PDAC with pathologic stage T1N0M0. Patients were excluded who received any neoadjuvant therapy or those with missing data on systemic therapy sequencing, those who received radiation, and patients with 90-day mortality. Patients who received AC were compared to those that received surgery alone.

Results: Of the 1,523 patients who met inclusion criteria for this study, 661 (43.4%) received AC and 862 patients (56.6%) underwent surgery alone. The majority of patients who received AC received single-agent (n=500, 75.6%) chemotherapy, while multi-agent chemotherapy was used in a minority of cases (n=130, 19.7%). However, multi-agent chemotherapy use is increasing, from 11.8% of patients who received any AC in 2012-2014 to 32.3% of patients in 2015-2017 ($p<0.001$). Patients who received AC were younger (67 years v. 71 years, $p<0.001$), had fewer comorbidities (Charlson-Deyo Score=0 in 67.9% v. 60.8%, $p=0.008$), and were more likely to have private insurance (39.3% v. 27.8%, $p<0.001$), compared with those treated with surgery alone. Patients in the AC group also had larger tumors (1.8 cm v. 1.5 cm, $p<0.001$) and higher rates of lymphovascular invasion (LVI) (11.8% v. 6.6%, $p=0.003$). There was no difference in tumor grade, initial CA 19-9, margin positivity rates, or type of pancreatectomy between the two groups. Patients who received AC had longer median overall survival (OS) compared with those who underwent surgery alone (104.3 mo v. 72.0 mo, $p<0.001$). To assess the impact of AC after accounting for available prognostic markers, a subset-analysis on patients (n=660, 43.3%) with complete data on available pathologic factors was performed (tumor size, grade, LVI, and margin status). On sequential Kaplan-Meier analysis of OS including only those with good prognostic factors (well to moderately differentiated tumors, margin-negative resection, LVI negative, and tumors < 1 cm in size), AC was associated with improved median OS in all subsets of patients (Table 1). In the cohort of patients with no adverse pathologic features (size < 1cm, margin negative, LVI negative, well to moderately differentiated tumors), there was a trend toward an improvement in median OS with AC (95.9 mo v. 90.6 mo, $p=0.095$). On multivariable analysis, factors associated with improved OS included receipt of AC, well-differentiated tumors, lower initial CA 19-9, Charlson-Deyo Score of 0, and an increased number of regional lymph nodes examined.

Conclusion: In patients with resected, Stage IA PDAC, AC is associated with improved survival, even in patients with good prognostic factors. Systemic chemotherapy should be utilized in all patients with PDAC.

Table 1 –Kaplan-Meier Analysis of Patients with Good Prognostic Factors

Tumor Characteristics	Number of Patients	Adjuvant Chemotherapy (Median OS, mo)	Surgery Alone (Median OS, mo)	p-value
Tumor Size < 1cm	208	95.9	78.2	**0.035**
LVI Negative	596	95.9	64.5	**0.001**
Well-Moderately Differentiated Tumors	537	95.9	63.1	**<0.001**
Margin Negative	641	95.9	64.1	**0.002**
No Adverse Pathologic Features	165	95.9	90.6	0.095

55. SINGLE-OPERATOR PERORAL PANCREATOSCOPY IMPROVES THE DIAGNOSTIC YIELD OF PREOPERATIVE WORKUP IN PRESUMED MAIN DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

S Vehviläinen, N Fagerström, R Valente, H Seppänen, M Udd, O Lindström, H Mustonen, F Swahn, U Arnelo, L Kylänpää

Presenter: Sini Vehviläinen | Helsinki University Hospital, Finland

Background: Distinguishing intraductal papillary mucinous neoplasms (IPMNs) from other pancreatic cystic lesions is important as IPMNs bear risk of becoming malignant. Especially distinguishing main pancreatic duct involving IPMNs (MD-IPMNs) with imaging can be difficult. In indefinite cases additional diagnostic measures are needed. Single-operator pancreatoscopy (SOP) has shown to be a promising method offering additional information about suspected lesions in the main pancreatic duct (MD). We aimed to establish the role of SOP in preoperative diagnostics of presumed MD-IPMNs. A secondary objective was to identify factors that contribute to SOP-related adverse events (AE).

Methods: A multicenter, part prospective but mostly retrospective study-cohort of 101 patients was gathered. In three centers, all patients undergoing SOP due to radiological suspicion of MD-IPMN were enrolled. As a primary outcome, the rate of how often the visual appearance of MD, and/or MD flushing liquid samples and biopsies taken during SOP affected further clinical care, was determined. As a secondary outcome, post-SOP complications according to Cotton consensus criteria, use of prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) and pancreatic stents and timing of pancreatic sphincterotomy (PS) were documented.

Results: We identified 86 (85%) patients, whose further care was affected by SOP. Based on SOP, surgery was planned for 29 (29%) patients. Cause for MD dilatation other than IPMN was found in 28 (28%) cases. In 35 (35%) patients SB-IPMN diagnosis without malignant or high grade dysplasia (HGD) was confirmed. AEs occurred 21 (21%) times, with pancreatitis (N&#3f19, 19%) being most common. Patients with prophylactic NSAIDs seemed to have a lower post-SOP pancreatitis rate compared to patients without prophylactic NSAIDs (8.0% vs 24%, p=0.146). Patients with prior PS had less moderate or severe post-SOP complications compared to patients who had their PS done in the same procedure (5.6% vs 21%, p=0.087). Furthermore, there was a decrease in moderate and severe pancreatitis rates in patients who had prophylactic NSAIDs and a prior PS compared to patients without prophylactic NSAIDs and a sphincterotomy done during SOP (5.6% vs 19.4%, p=0.238). Patients with a prophylactic pancreatic stent had a slightly lower rate for post-SOP pancreatitis compared to patients without pancreatic stents (16% vs 23%, p=0.456). However, due to low number of AEs, statistically significant correlation between AEs and use of prophylactic NSAIDs and pancreatic stents, or timing of PS could not be established.

Conclusion: SOP aids clinical decision-making in presumed MD-IPMNs. Risk for AEs should be considered. Larger cohort is needed to validate factors contributing to AEs.

56. IMPACT OF LYMPH NODE RATIO ON SURVIVAL IN THE HISTOPATHOLOGICAL SUBTYPES OF RESECTED AMPULLARY CANCER: A RETROSPECTIVE INTERNATIONAL MULTICENTER COHORT STUDY

D Lemmers, G Malleo, K Khalil, S Robinson, G Nappo, G Gradinariu, M Bonds, A Halimi, M Mortimer, VK Mavroeidis, N Napoli, F Burdio, L Bolm, U Wellner, P Pessaux, B Ielpo, U Boggi, Z Soonawalla, B Al-Sarireh, NB Jamieson, L Zarantonello, T Armstrong, A Als

Presenter: Daniel Lemmers MD | Fondazione Poliambulanza, Italy

Background: Ampullary adenocarcinoma (AAC) is a rare malignancy with extensive morphological heterogeneity. Variable results have been reported regarding the predictive value of lymph node ratio (LNR) on survival in patients with resected AAC. The aim of this study was to investigate the prognostic predictive value of LNR adjusted for factors influencing survival in patients with resected AAC.

Methods: This retrospective international multicenter cohort study included all patients who underwent pancreatoduodenectomy for AAC (2006-2020). Patients who underwent palliative procedures or local excision of AAC were excluded, as were patients with an R2 resection, distant metastasis, or 30-day postoperative mortality. Overall survival(OS) was assessed using the Kaplan-Meier method and log-rank tests. Cox proportional hazard models were performed to identify independent predictors of OS. Optimal cut-off for LNR was determined calculating the Youden's index and logrank test.

Results: Overall, 1230 patients after pancreatoduodenectomy for AAC were included. Histopathologic subtype was documented in 907 patients (73.7%), of whom 369 had intestinal subtype (40.7%), 477 pancreaticobiliary subtype (52.6%), and 61 a mixed subtype (6.7%). Median survival was not reached for the intestinal subtype. For the pancreatobiliary subtype and mixed subtype, median survival was 60 (42-77), and 76 (35-116) months, respectively. The optimal cut-off for the LNR was 0.10. Age, tumor size, resection margin, T3/4 stage, poor tumor differentiation, and LNR were independent predictors of survival (Table 1).

Conclusion: This study shows the importance of LNR for prognosis in patients with all histopathological subtypes of resected AAC and an optimal cut-off point for the LNR of 0.10.

Table 1. Multivariable Analysis identifying Risk Factors Associated With Overall Survival According to the Cox Proportional Hazard Model

	Hazard Ratio	[95% CI]	P Value
Age	1.028	(1.017-1.040)	**<0.001**
Tumor size	1.011	(1.003-1.019)	**0.006**
Resection margin	1.295	(1.012-1.655)	**0.040**
Perineural invasion	1.036	(0.820-1.310)	0.765
Lymphovascular invasion	1.193	(0.972-1.536)	0.171
T stage 3/4	1.614	(1.241-2.097)	**<0.001**
Tumor differentiation*	1.297	(1.058-1.589)	**0.012**
LNR			
LNR 0-0.1	1.433	(1.020-2.012)	**0.038**
LNR >0.1	3.289	(2.485-4.401)	**<0.001**

*Compared with well and moderate differentiated tumor,

The bold values represent statistically significant values.

CI = Confidence Interval

57. RATIONALE OF USING THE COMBINATION OF ANTI-PD-1 ANTIBODY AND ANTI-IL-8 ANTIBODY FOR THE PANCREATIC CANCER TREATMENT

P Li, N Rozich, JX Wang, JK Wang, Y Xu, B Herbst, R Yu, S Muth, N Niu, KY Li, V Fune, J Gai, A Osipov, C Wolfgang, L Ming, TB Liang, L Zheng

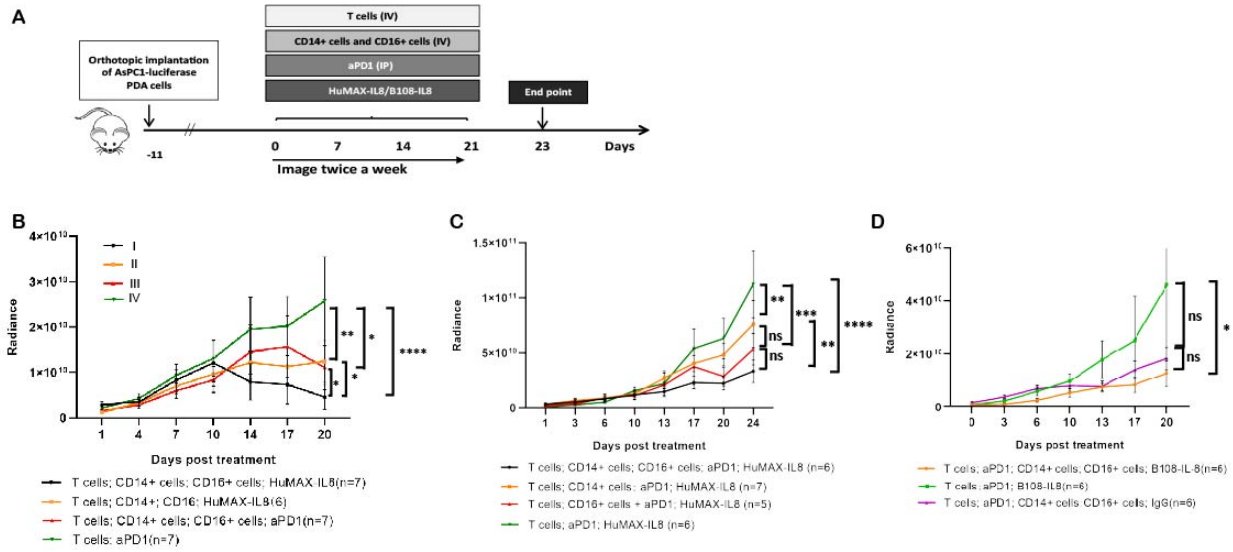
Presenter: Pan Li | Johns Hopkins University School of Medicine, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) does not respond to the immune checkpoint inhibitors (ICI) as single agent treatments including anti-PD-1 antibody. One of the mechanisms for the resistance of PDAC to ICI is now recognized to lie in the immunosuppressive microenvironment (TME) in PDAC. Myeloid cells were thought to be immunosuppressive cells in the TME. Human interleukin-8 (IL-8) is a pro-inflammatory chemokine in the CXC family and has the capability of recruiting myeloid cells into the TME to promote tumor progression and immune escape. Therefore, several anti-IL-8 blockade antibodies were developed including HuMax-IL8 and B108-IL8, which both are fully human IgG1 kappa monoclonal antibodies. We therefore tested whether anti-IL-8 antibodies can potentiate anti-tumor activity of anti-PD-1 antibody in a humanized model of PDAC.

Methods: We reconstituted the immune system of the NGS mice with ex vivo activated human T cells and a combination of CD14+ and CD16+ myeloid cells after the mice were orthotopically implanted with human PDAC cells. Our results showed that anti-PD-1 antibody alone had minimal anti-tumor activity when mice were reconstituted with ex vivo activated T cells.

Results: Interestingly, the infusion of the combination of CD14+ and CD16+ myeloid cells together with anti-PD-1 antibody resulted in a modest anti-tumor activity. Adding either HuMAX-IL8 or B108-IL8 led to a significantly enhanced anti-tumor activity. Both CD14+ and CD16+ myeloid cells appeared to be needed for the full anti-tumor activity of IL-8 blockade because mice infused with only CD14+ myeloid cells did not respond to IL-8 blockade and mice infused with only CD16+ myeloid cells responded partially to IL-8 blockade. This result suggested that the target of IL-8 is mainly present in CD16+ myeloid cells and is likely to be granulocytes. Tumor-infiltrating immune cells were isolated and demonstrated that IL-8 blockade increases CD45+CD11b+CD15+CD14- myeloid cells, which is known to be comprised by neutrophils and granulocytic myeloid derived suppressive cells (G-MDSC), in the tumors. Reconstitution of the mice with myeloid cells led to a decrease of CD8+ T cells in the tumors; however, IL-8 blockade brought the CD8+ T cell number back to the baseline. Consistent with an effect of IL-8 blockade on the increase of CD15+CD14- myeloid cells, single nuclear RNA sequencing analysis of the tumor tissues showed that the innate immune response and cytokine response pathways in the myeloid cell cluster were activated by IL-8 blockade. This result suggested that IL-8 blockade did not simply inhibit myeloid cells as previously anticipated, but potentiated myeloid cells for the innate immune response and the production of type I cytokines. Such immune responses may subsequently activate the effector T cells as the single nuclear RNA sequencing analysis did show enhanced activation signals in the T cell cluster from the tumors treated by anti-IL-8 antibodies.

Conclusion: Taken together, this study supports further testing of anti-IL-8 antibodies including B108-IL8 and HuMax-IL8 in combination with anti-PD-1 antibodies for PDAC treatment.


A
T cells (IV)
CD14+ cells and CD16+ cells (IV)
aPD1 (IP)
HuMAX-IL8/B108-IL8
End point
Orthotopic implantation of AsPC1-luciferase PDA cells
-11
0
7
14
21
23
Days
Image twice a week
B
Radiance
Days post treatment
I
II
III
IV
T cells; CD14+ cells; CD16+ cells; HuMAX-IL8(n=7)
T cells; CD14+; CD16: HuMAX-IL8(6)
T cells; CD14+ cells; CD16+ cells; aPD1(n=7)
T cells: aPD1(n=7)
C
Radiance
Days post treatment
ns
T cells; CD14+ cells; CD16+ cells; aPD1; HuMAX-IL8 (n=6)
T cells; CD14+ cells; aPD1; HuMAX-IL8 (n=7)
T cells; CD16+ cells + aPD1; HuMAX-IL8 (n=5)
T cells; aPD1; HuMAX-IL8 (n=6)
D
Radiance
Days post treatment
ns
T cells; aPD1; CD14+ cells; CD16+ cells; B108-IL-8(n=6)
T cells; aPD1; B108-IL8(n=6)
T cells; aPD1; CD14+ cells CD16+ cells; IgG(n=6)

58. A CROSS-VALIDATION OF PERIOPERATIVE THERAPY CONCEPTS IN THE NATIONAL CANCER DATABASE (NCDB) AND THE GERMAN CANCER REGISTRY OF THE WORKING GROUP OF GERMAN CANCER CENTERS (WGCC/ADT)

N Petruch, L Bolm, S Zemskov, M Zeller, T Baba, J Roldan, JM Harrison, E Petrova, H Lapshyn, R Braun, KC Honselmann, AV Kirichenko, D Rades, T Keck, C Fernandez-del Castillo, UF Wellner, RE Wegner
Presenter: Natalie Petruch | Massachusetts General Hospital, United States

Background: The aim of this study is to assess the concepts and outcome of perioperative treatment regimens in stage IA-III pancreatic cancer (PDAC) in a cross-validation of the German Cancer Registry of the German Working Group of Cancer Centers (WGCC/ADT) and the National Cancer Database (NCDB).

Methods: Patients undergoing oncologic resection for clinical stage IA-III PDAC with either operation alone (OP), neoadjuvant therapy and operation (neo+OP), operation and adjuvant therapy (OP+adj) and neoadjuvant therapy, operation and adjuvant therapy (neo+OP+adj) were identified from the WGCC/ADT and NCDB databases between 2000 and 2018. Patient baseline characteristics, histopathological parameters and long-term overall survival (OS) after resection were evaluated. Long-term overall survival rates (OS) associated with perioperative treatment regimens were analyzed by Kaplan Meier method and Cox regression after prospensity score-based matching.

Results: A total of 1611 patients from the WGCC/ADT database and 29081 patients from the NCDB with oncologic resection for stage IA-III PDAC were included. While neo+OP and neo+OP+adj failed to show a benefit in OS as compared to OP alone for stage IA-IIA patients in the WGCC/ADT registry, OS rates were improved for stage IIB-III patients with neo+OP (10.0m vs. 18.2m, HR 0.746, 95%CI 0.530-0.978, p=0.043) and neo+OP+adj (10.0m vs. 19.9m, HR 0.559, 95%CI 0.398-0.784, p=0.010). In both stage IA-IIA and stage IIB-III patients neo+OP (p<0.001) and neo+OP+adj (p<0.001) improved OS rates as compared to OP alone in the NCDB registry. Neo+OP was associated with prolonged overall survival rates as compared to OP+adj for both stage IA-IIA (27.1m vs. 25.3m, HR 1.066, 95%CI 1.010-1.126, p<0.001) and IIB-III patients (25.8m vs. 20.8m, HR 1.305, 95%CI 1.225-1.390, p<0.001). In the NCDB registry, neo+OP+adj was associated with improved OS rates as compared to neo+OP for both stage IA-IIA (27.1m vs. 36.6m, HR 0.716, 95%CI 0.614-0.836, p<0.001) and IIB-III patients (25.8m vs. 28.6m, HR 0.860, 95%CI 0.717-0.978, p<0.001). There was no difference in overall survival for either stages between neo+OP and neo+OP+adj in the WGCC/ADT registry. Neoadjuvant radiochemotherapy was not associated with an improved OS as compared to neoadjuvant chemotherapy alone in either registry.

Conclusion: The cross-validation study of the NCDB and WGCC/ADT registries demonstrated a survival benefit with neoadjuvant therapy in both stage IA-IIA and stage IIB-III PDAC. Neoadjuvant therapy combined with adjuvant therapy is associated with improved overall survival as compared to neoadjuvant or adjuvant therapy alone. Concepts and outcomes of perioperative therapy remained widely consistent in both registries.

59. A SIMPLE RISK SCORE FOR DETECTING RADIOLOGICAL OCCULT METASTASIS IN PATIENTS WITH RESECTABLE OR BORDERLINE RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA

D Hashimoto, S Satoi, T Sakagucui, T Yamamoto, S Yamaki, S Hirooka, M Ishida, T Ikeura, K Inoue, M Sekimoto

Presenter: Daisuke Hashimoto MD, PhD | Kansai Medical University, Japan

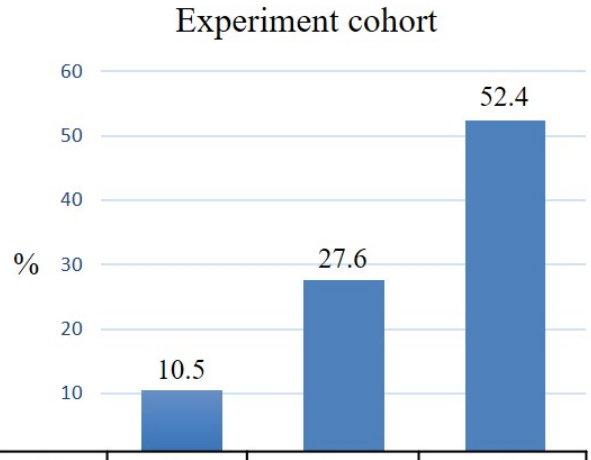
Background: Although improved survival has been reported in patients treated with multimodality treatment combined with margin-negative resection, only 15–20% of patients with pancreatic ductal adenocarcinoma (PDAC) are candidates for surgical intervention. Among these patients, 14–30% are found to have unresectable disease at the time of surgery. Small metastatic lesions can be missed during preoperative screening, resulting in unbeneficial laparotomy. We previously advocated carbohydrate antigen (CA) 19-9 ≥ 150 U/mL and tumor size ≥ 30 mm as "high-risk markers" for predicting unresectability among patients with radiologically resectable (R) or borderline resectable (BR) PDAC.
The aims of this study were to identify new predictors of OAM and establish a risk scoring system for detecting OAM in patients with R/BR PDAC.

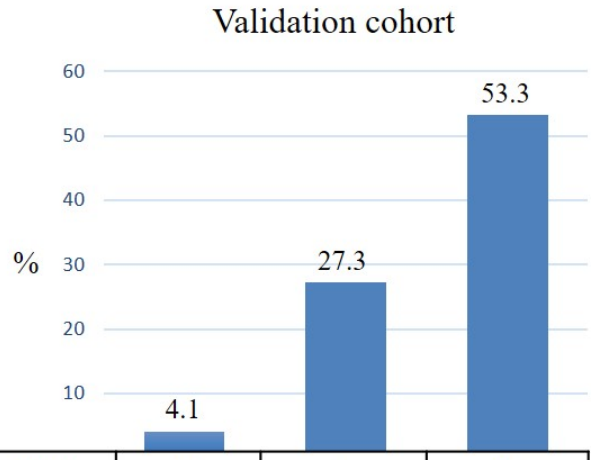
Methods: A single-institution, retrospective study was conducted using a prospectively recorded database of patients who were treated for PDAC between January 2006 and December 2020. Predictors of OAM were investigated retrospectively in an experiment cohort from 2006 to 2018. The proposed risk scoring system was validated in another cohort from 2019 to 2020

Results: In total, 513 patients with R/BR PDAC who underwent surgical evaluation of OAM were included in this study and divided into the experimental cohort (405 patients) and the validation cohort (108 patients) chronologically. OAMs were detected in 22% of the experimental cohort and 19% of the validation cohort; this difference was not significant. In the experimental cohort, the current criteria consisting of CA19-9 and tumor size revealed the weak point that OAM was still found in 17% even in the low-risk group (CA19-9 level less than 150 U/mL and/or tumor size less than 30 mm). Univariate analysis of considerable predictors for OAM among pre-operative parameters in the experimental cohort revealed that tumor location in the body/tail ($p < 0.0001$), high-risk markers ($p < 0.001$), and serum CEA greater than 5 ng/mL ($p = 0.0073$) were significant predictors for OAM. Multivariate analysis identified tumor location of body/tail (odds ratio [OR] 4.45, $p < 0.0001$) and "high-risk markers" (OR 2.07, $p = 0.011$) as independent predictors of OAM. Based on this result, a scoring system was constructed consisting of body/tail (yes: 1, no: 0) and "high-risk markers" (yes: 1, no: 0). As increasing scores, the incidence of OAM was elevated in the validation cohort (Figure). Moreover, when staging laparoscopy (SL) was performed for patients with scores 1/2 in the validation cohort, the eligibility for SL, sensitivity, and negative predictive value of OAM were 55%, 91%, and 96%, respectively. Thus, the efficacy of the scoring system was validated well.

Conclusion: In conclusion, tumor location in the pancreatic body/tail and a combination of CA19-9 level greater than or equal to 150 U/mL and tumor size greater than or equal to 30 mm at the biliary decompression before NAT were found to be independent predictors of OAM in patients with R/BR PDAC. This new and simple OAM scoring system is reproducible and easy to use in the clinical setting.

Risk score and percentage of OAM in each cohort





Score	0	1	2
Location/ Risk	Ph / Low	Ph / High Pbt / Low	Pbt / High
Total, n	200	163	42
OAM, n	21	45	22
OAM,%	10.5%	27.6%	52.4%

Score	0	1	2
Location/ Risk	Ph / Low	Ph / High Pbt / Low	Pbt / High
Total, n	49	44	15
OAM, n	2	12	8
OAM,%	4.1%	27.3%	53.3%

60. THE TUMOR IMMUNE MICROENVIRONMENT IS DECISIVE IN THE SURVIVAL OF PANCREATIC DUCTAL ADENOCARCINOMA

H Aziz, L Saida, A Stubbs, Y Li, K Sideras, W de Koning, CHJ van Eijck, DAM Mustafa
Presenter: Dana Mustafa MD | Erasmus University Medical Center, Netherlands

Background: Only 9% of the patient survive longer than 5 years. So far, factors underlining long-term survivorship in PDAC are not well understood. Therefore, we aimed to study the key players in the tumor immune microenvironment (TIME) that are associated with long-term survivorship in PDAC patients.

Methods: The immune-related gene expression profiles of surgically resected PDAC patients who survived and remained recurrence-free of disease for > 3 years (long-term survivors, n=10) were compared to that of PDAC patients who had a recurrence of disease and survived ≤ 6 months (short-term survivors, n=10). Samples were profiled using the PanCancer Immune Profiling Panel of NanoString Technology. Validation was performed by spatial analysis of immune cells using the GeoMx Digital Spatial Profiler (DSP).

Results: Tumor-infiltrating B cells were found to be significantly increased in the TIME of long-term survivors by gene expression profiling (p=0.018). The high infiltration of B cells was confirmed by spatial protein profiling (p=0.008). Interestingly, this increase was associated with more T cell and antigen-presenting cell infiltration. Moreover, the activated immune cells were found to infiltrate in between tumor cells as well as in stromal areas. Contrastingly, the TIME of short-term survivors was characterized by a high density of immunosuppressive cells like CD25 and regulatory T cells infiltrating in a highly fibrotic vicinity.

Conclusion: This is the first comprehensive study that connects the immune landscape at the gene expression and protein spatial infiltration to the survivorship of PDAC patients. Our findings highlight the importance of B cell-based therapy for future individualized immunotherapy in PDAC patients.

61. KRAS MUTATION ALLELE FREQUENCY IMPACTS PROGNOSIS IN PANCREATIC DUCTAL ADENOCARCINOMA USING NEXT-GENERATION SEQUENCING

DO Nauheim, D Moskal, B Renslo, W Jiang, C J Yeo, A Nevler, WB Bowne, H Lavu
Presenter: David Nauheim | Thomas Jefferson University, United States

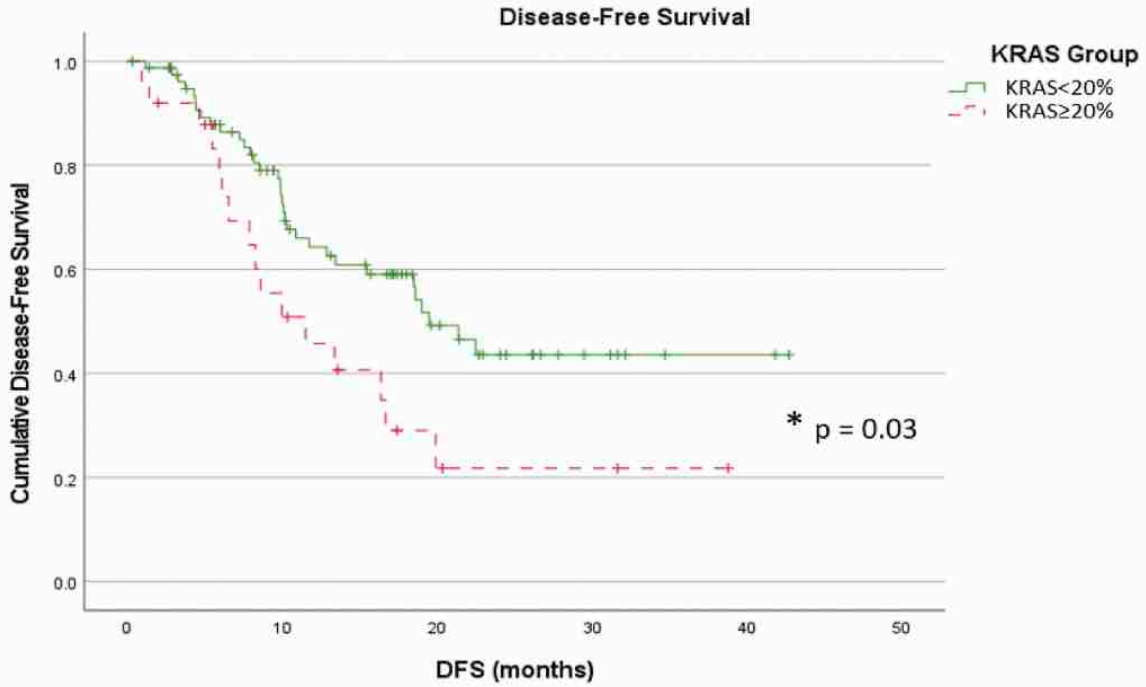
Background: NGS (Next-Generation Sequencing) provides detailed data on genetic mutations as well as mutant allele frequency in resected tumor specimens. We investigate the prognostic significance of KRAS mutant allele frequency in patients with Pancreatic Ductal Adenocarcinoma (PDAC).

Methods: A retrospective study reviewed patients who underwent surgical resection for PDAC and analyzed tumors with an in-house mutational panel. Tumor specimens were micro-dissected and separated from adjacent stromal tissues. Micro-dissected samples were studied using an NGS-based assay to detect over 200 hotspot mutations in 42 genes (Pan42) commonly involved in PDAC.

Results: In this study, 144 patients with Pan42 genomic analysis between 2015 and 2020 were evaluated. Overall, the median survival after surgery was 29.1 months. 121 patients (84%) harbored a KRAS mutation. Detected mutant allele frequencies in PDAC were categorized as less than 20% (KRAS < 20%, n= 92) or greater than or equal to 20% (KRAS ≥20%, n= 29). KRAS ≥20% patients were noted to have a significantly poorer disease-free survival (DFS) after surgery (11.5 ± 2.1 vs. 19.5 ± 3.5 months, p = 0.03). On univariate analysis, KRAS ≥20% patients had more advanced tumor stage (p = 0.02), larger tumors (3.6 vs 2.7 cm, p = 0.001), greater tumor cellularity (26% vs 18%, p = 0.001) and higher rate of distant recurrence (p = 0.03). Multivariate analysis showed KRAS ≥20% and perineural invasion as independent predictors for DFS (HR = 2.4, p = 0.01).

Conclusion: This study demonstrates the importance of KRAS mutant allele frequency on pathological characteristics and prognosis in PDAC.

Figure: PDAC Disease Free Survival Based on KRAS Mutant Allele Frequency



62. STAT3 SIGNALING INHIBITION IN REGULATORY T CELLS IMPROVES IMMUNE RESPONSE TO RT IN PDAC

M Piper, B Van Court, A Mueller, D Nguyen, J Gadwa, T Bickett, R Schulick, W Messersmith, M Del Chiaro, K Goodman, F An, A Dent, RM Kedl, L Lenz, SD Karam

Presenter: Miles Piper BS | University of Colorado, United States

Background: Treatment failure in PDAC arises from multiple inherent and adaptive biological origins, one of the most significant being immunosuppressive resistance characterized by tumor microenvironment (TME) infiltration of suppressive populations including myeloid derived suppressor cells (MDSCs) and Tregs. Tumor infiltrating Tregs have been found to correlate with a worsened prognosis, but targeted Treg depletion has been met with varying results. We therefore rationalized that treatments aimed at inhibiting, rather than depleting, Tregs may result in a more robust response. Various immune modulating agents, including radiation therapy (RT), have been utilized in an attempt to invigorate an immune response and overcome Treg-mediated immunosuppression in PDAC. However, when used as a single agent, this treatment modality has been met with limited efficacy. As Treg-expressed STAT3 has been shown to be a critical mediator of FoxP3, TGF-β, and IL-10 expression, we hypothesized that the immunosuppressive nature of the TME in PDAC, and the resulting therapeutic resistance to RT, can be overcome by targeting the suppressive activity of Tregs through STAT3 signaling inhibition.

Methods: Patient PDAC tissue samples were subjected to RNA sequencing and cell type composition analysis to identify changes in immune infiltration following RT. Local and metastatic orthotopic in vivo tumor models of PDAC were used to characterize disease progression and response to treatment. Flow cytometry was used to analyze frequency and activation state of tumor infiltrating, circulating, and nodal immune populations. STAT3 inhibition was accomplished using a synthetic anti-sense oligonucleotide (ASO) targeting murine STAT3. Various genetically engineered mouse models, including FoxP3 Cre/STAT3 fl, NKp46 Cre/STAT3 fl, DEREG, and Batf3-/- strains, were used to understand mechanisms of response.

Results: Although increasing the infiltration and activation of dendritic cells (DCs) in PDAC patients, RT also resulted in an increase in Treg infiltration, which was correlated with a lack of intratumoral natural killer (NK) and CD8 T cell infiltration. Using multiplexed IHC on human samples, as well as flow cytometry on murine tumors, STAT3 expression was found to be increased on intratumoral Tregs post-RT, making it a valid target for inhibition. Knockout of STAT3 on Tregs using genetically engineered mouse models, as well as pharmacologic inhibition of Treg-expressed STAT3 using a small molecule inhibitor, resulted in multicompartmental immune activation, a reduction in circulating tumor cells (CTCs), and enhanced control of local and distant disease, but only when used in combination with RT. We found both a significant decrease in intratumoral Tregs and a significant increase in tumor-infiltrating DCs, as well as systemic activation of NK, CD4, and CD8 T cells, following STAT3 ASO + RT treatment over control. Further, through genetic and antibody-mediated depletion, we found that the improved response to STAT3 inhibition and RT treatment is dependent on the activity of both DCs and NK cells.

Conclusion: Our data are supportive of the notion that Treg inhibition results in increased activation of effector populations and an improved survival advantage, further suggesting that Treg-targeted therapies may be useful in improving response to RT in pancreatic cancer.

63. SUSCEPTIBILITY TO IMMUNE ELIMINATION OF EPITHELIAL AND QUASI-MESENCHYMAL PANCREATIC DUCTAL ADENOCARCINOMA CELLS UNDER BASAL CONDITIONS AND FOLLOWING TREATMENT WITH FOLFIRINOX

Y Sekigami, S Arya, D Vallera, V Deshpande, DT Ting, S Ferrone, CR Ferrone
Presenter: Yurie Sekigami MD | Massachusetts General Hospital, United States

Background: Pancreatic ductal adenocarcinoma (PDAC) exists as epithelial (E) and quasi-mesenchymal (QM) subtypes, with the latter conferring increased chemoresistance. The differential sensitivity of E and QM PDAC to chemotherapy has prompted us to investigate whether these subtypes also differ in their sensitivity to antibody-mediated lysis under basal conditions and following incubation with FOLFIRINOX, which has been shown to shift PDAC towards the QM state. B7-H3 was used as the tumor antigen (TA) target. NK cells (tri-specific killer engagers) and T cells (CAR) were used as effectors.

Methods: E (PDAC6) and QM (PDAC8, PDAC9) cell lines were used as targets both under basal conditions and following a 96-hour incubation with FOLFIRINOX. The TriKE construct containing anti-CD16 scFv and anti-B7-H3 scFv linked by IL-15 and the B7-H3 CAR were generated as described. PDAC cells were incubated with effector cells for up to 72 hours. Viability was assessed by MTT and flow cytometric analysis (FACS). FACS and monoclonal antibody 376.96 were used to assess B7-H3 expression.

Results: While the susceptibility of all untreated cell lines to immune elimination was variable, there was no association with the E/QM subtype. Both subtypes were sensitive to immune lysis, and all PDAC cell lines became more susceptible to elimination following incubation with FOLFIRINOX by at least 23% (Figure). This increased susceptibility does not reflect target TA upregulation as no change was detected in B7-H3 expression on cells incubated with FOLFIRINOX.

Conclusion: FOLFIRINOX induced increased susceptibility of PDAC cells to immune elimination irrespective of subtype and target TA expression.

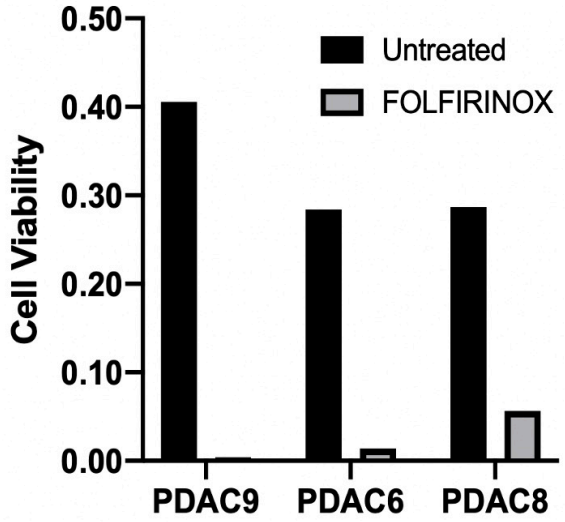


Figure. Enhancement by FOLFIRINOX of the susceptibility of patient-derived PDAC cell lines to elimination by B7-H3 TriKEs. Untreated PDAC cells and PDAC cells incubated with FOLFIRINOX for 96 hours were co-cultured with NK cells at an E:T of 5:1 for 48 hours in the presence of 100 nM B7-H3/IL-15 TriKEs. Cell viability was assessed by MTT assay.

64. HEATING UP A COLD TUMOR: HYPERGLYCEMIA SENSITIZES PANCREATIC CANCER TO SYSTEMIC THERAPIES

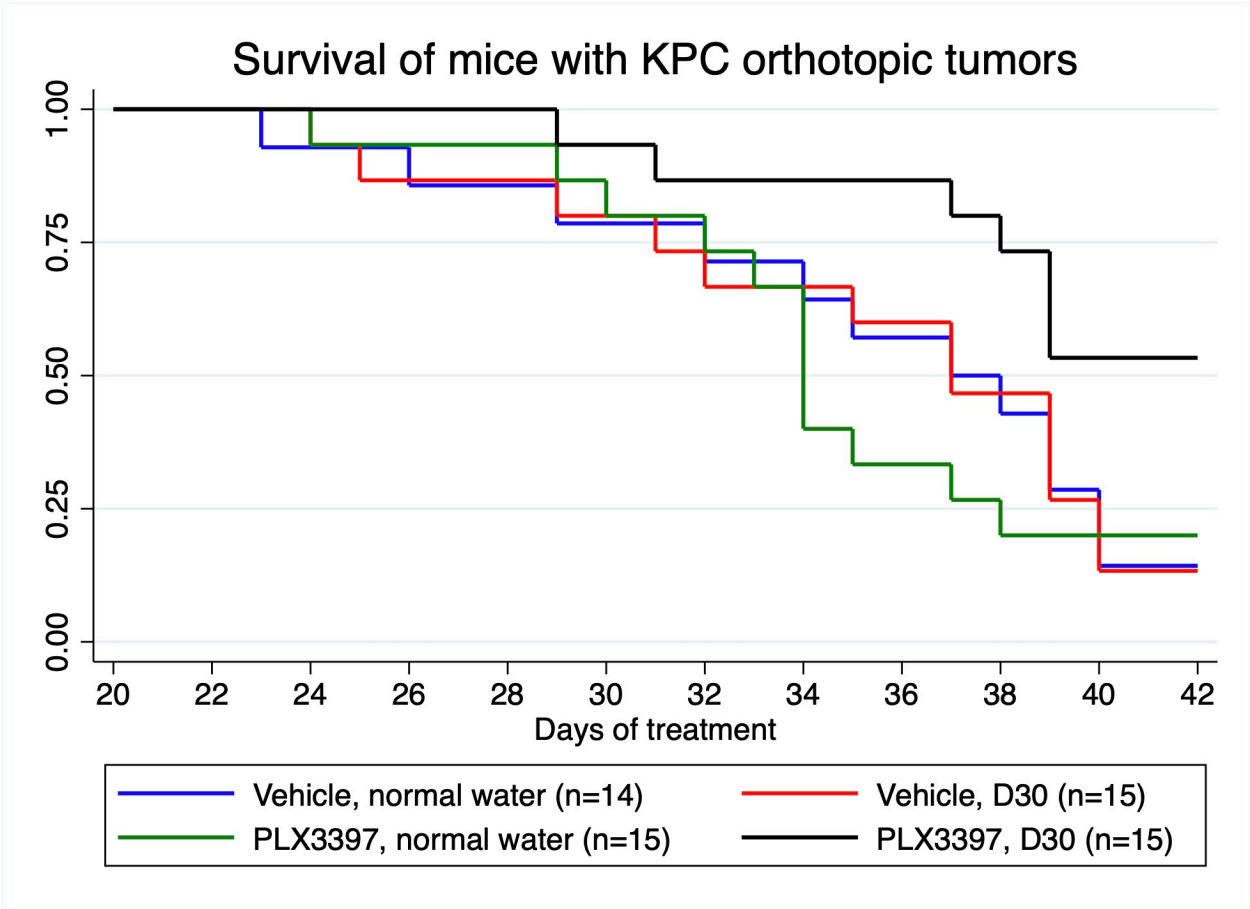
JJ Hue, A Vaziri-Gohar, M Zarei, HJ Graor, O Hajihassani, ES Katayama, LD Rothermel, JM Winter
Presenter: Jonathan Hue MD | University Hospitals Cleveland Medical Center, United States

Background: Pancreatic cancer (PC) cells thrive in hypoglycemic conditions found within the tumor microenvironment. This harsh landscape is not conducive to anti-tumor immune cell function, which are reliant on high glucose concentrations for energy production via glycolysis. PC is a "cold" tumor. Thus, existing immunotherapies have been largely ineffective to date. Herein, we attempt to augment the effectiveness of systemic therapies in a PC model by inducing a hyperglycemic state.

Methods: Macrophages derived from immunocompetent mice were cultured in low glucose conditions consistent with the tumor microenvironment (2.5 mM glucose) or hyperglycemic conditions (25 mM). Macrophages were polarized towards an "M1" anti-tumor phenotype or "M2" pro-tumor phenotype. Murine PC cells (KPC) were cultured in similar conditions. Phenotypic, metabolic, and cell survival assays were performed. For in vivo survival studies, KPC cells were orthotopically injected into the tail of the pancreas of immunocompetent mice. Mice were randomized to different treatment arms after tumor validation. Mice were provided with normal water or 30% dextrose water (D30) ad lib and were administered PLX3397 (a CSF1R macrophage inhibitor) or vehicle, totaling four groups. Survival was measured from time of treatment initiation and compared with the log-rank test.

Results: Consistent with differences in basal metabolism, there was a 3-fold reduction in cell culture glucose concentrations with M1 macrophages (glycolytic); however, glucose concentrations remained fairly stable with M2 macrophages (oxidative phosphorylation) over a 5-day experiment. As cell culture glucose concentrations decreased, there was a 30% reduction in M1 macrophage viability. Conversely, M2 macrophages survived better in low glucose conditions. Using a co-culture cell growth assay, there was a 95% reduction in KPC cell growth when cultured with M1 macrophages, relative to KPC cells alone. But, there was a 30% increase in KPC cell growth when co-cultured with M2s. The addition of PLX3397 had a rescue effect for anti-tumor M1 cell viability and M1 polarization (assessed via increased protein levels of nitric oxide, an M1 phenotypic marker). PLX3397 reduced pro-tumor M2 cell viability and M2 polarization (reduced protein levels of arginase, an M2 phenotypic marker). Using flow cytometry, we further validated a reduction in M2 polarization as the proportion of non-M2 macrophages (double negative for CD206 and CD301, both M2 markers) increased from 26.1% to 42.2% with the addition of PLX3397 in high glucose conditions. Lastly, KPC tumors were surgically implanted into the pancreas of immunocompetent mice. The peripheral glucose levels of mice receiving D30 was approximately 100 mg/dL higher relative to normal water (~300 vs 200 mg/dL, $p<0.05$) over the course of the experiment. The median survival for mice receiving PLX3397 and regular water was 34 days. Median survival for mice receiving PLX3397 and D30 has not been reached as of day 42 of treatment ($p=0.01$, Figure).

Conclusion: Anti-tumor M1 macrophages appear to survive and function better in higher glucose environments. Forced hyperglycemia in addition to PLX3397 may be a promising combination for patients with pancreatic cancer. These findings are important as we are likely at least several years away from development and approval of a new paradigm-shifting therapy.


Survival of mice with KPC orthotopic tumors
1.00
0.75
0.50
0.25
0.00
20
22
24
26
28
30
32
34
36
38
40
42
Days of treatment
Vehicle, normal water (n=14)
Vehicle, D30 (n=15)
PLX3397, normal water (n=15)
PLX3397, D30 (n=15)