P 1. NEOADJUVANT THERAPY UTILIZATION FOR PANCREATIC CANCER AMONG HIGH VOLUME SURGICAL CENTERS: IS IT A MARKER OF QUALITY?

AV Fisher, DE Abbott, SA Campbell-Flohr, S Ronnekleiv-Kelly, CC Greenberg MD, ER Winslow, SM Weber
University of Wisconsin

Background: Many surgeons advocate the use of neoadjuvant treatment for resectable pancreatic cancer, however little is known about variation in the utilization of neoadjuvant therapy at the hospital level.

Methods: The National Cancer Data Base was used to identify patients undergoing resection for pancreatic cancer between 2006-2014 at high volume centers performing >10 pancreatectomies annually. Hospitals were grouped by neoadjuvant therapy (NAT) utilization using standard deviations (sd) from the mean as follows: high NAT utilizers (>2 sd above the mean, >40% of patients receiving NAT), medium-high (1-2 sd, 27-40%), medium (0-1 sd, 14-26%), or low (-1.1-0 sd, <14%). Outcomes were compared across NAT utilization groups using the Kaplan-Meier method and a multi-level mixed-effects survival model which adjusted for hospital random-effects. Cox proportional hazards modelling was performed to identify predictors of overall survival (OS).

Results: Of 20,119 patients undergoing resection at 107 high volume centers, 2,952 (14.7%) received NAT. The proportion of patients receiving NAT varied widely among hospitals, ranging from 0% to 74.2%, with only five centers using NAT in >40% of patients. These five hospitals had the longest median OS at 28.9 months, compared to 21.1 months for low NAT utilizers ($p<0.001$, Figure 1a). The survival difference was even greater when using the mixed-effect survival model which accounted for random hospital effects (median OS 33.5 mo. for high NAT utilizers vs. 23.4 mo. for low NAT utilizers, $p<0.001$, Figure 1b). R0 resection occurred more frequently at high neoadjuvant centers (86% vs 77% at low neoadjuvant centers, $p<0.001$). On multivariable analysis, high and medium-high neoadjuvant utilization predicted improved OS with HR 0.86 [0.77-0.95, $p=0.003$] and HR 0.89 [0.83-0.96, $p=0.002$] respectively, compared to low utilizers. After excluding patients who underwent neoadjuvant therapy, there remained an association of improved OS in high neoadjuvant utilization hospitals (25.3 months vs 20.7 months, $p<0.001$).

Conclusion: High volume hospitals that more commonly utilize neoadjuvant therapy demonstrate longer survival for all patients treated at those centers, whether or not they received neoadjuvant therapy. High neoadjuvant utilization may be a marker of institutional processes and/or structural factors that contribute to improved outcomes, but further studies are needed to define these factors.

Figure 1: Unadjusted Kaplan-Meier and Adjusted Parametric Survival Curves by Hospital Neoadjuvant Utilization Group

Figure 1a:

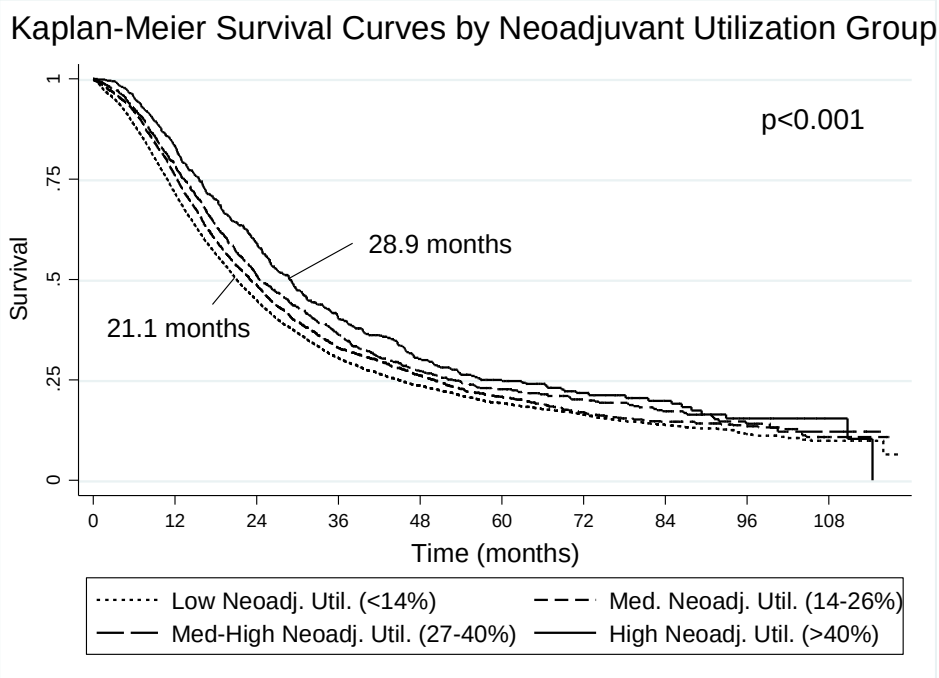


Figure 1b:

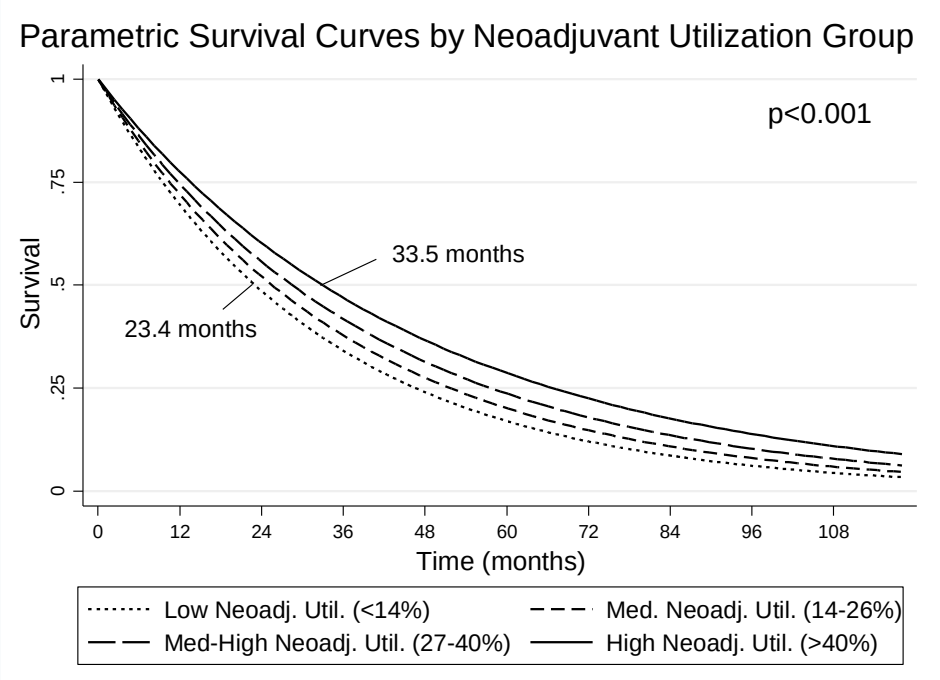


Figure 1a: Unadjusted Kaplan-Meier survival curves by hospital neoadjuvant utilization group.
Figure 1b: Age-adjusted parametric survival curves by neoadjuvant utilization group using mixed-effect model with random hospital-effect.

P 2. THE ROLE OF PATIENT AGE IN THE MANAGEMENT OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS: SAME RISK OF CANCER-RELATED DEATH BUT DIFFERENT IMPLICATIONS FOR THE MANAGEMENT

S Andrianello, G Marchegiani, G Perri, T Pollini, M Biancotto, G Malleo, C Bassi, R Salvia

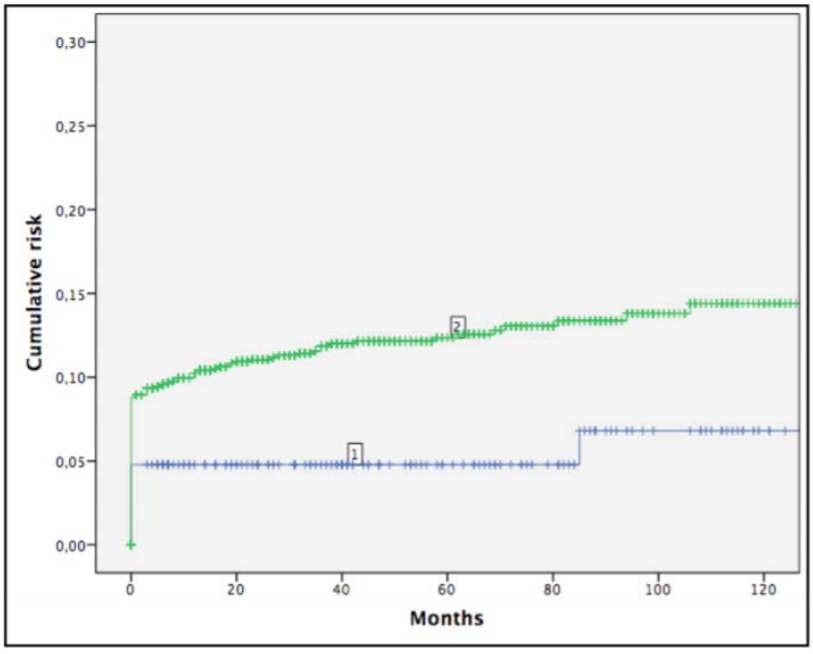
Verona University

Background: Little is known regarding the natural history of Intraductal Papillary Mucinous Neoplasms (IPMNs) of the pancreas diagnosed in younger individuals, as current guidelines only suggest surgery in younger patients. The aim of this study was to evaluate whether clinical features and malignancy risk of IPMNs are influenced by patient's age at diagnosis.

Methods: A total of 2189 progressively observed IPMNs were retrieved and dichotomized, according to a 50-year-old cut-off. Surgically resected IPMNs were compared in terms of pathological features. Both surgically resected and follow-up patients were compared in terms of cumulative risk of developing high-risk stigmata (HRS), overall survival (OS) and disease-free survival (DSS), considering the occurrence of pancreatic cancer (PC).

Results: Patients <50 years old had more frequent abdominal pain (38.5 vs. 22.4%; p<0.01) and acute pancreatitis (20.4 vs. 9.3%; p<0.01) at presentation. Patients >50 years old had more multifocal IPMNs (50 vs 36.9%; p<0.01) and more frequent HRS (8.5% vs 4.3%; p 0.04). Among resected patients, those >50 years had more invasive IPMNs (26.6% vs 17.3%; p 0.03). Patients >50 years had a significantly higher cumulative risk of developing HRS during that time, a significantly lower OS, but similar DSS when compared with those <50 years old.

Conclusion: The natural history of IPMNs in terms of cancer-related death does not seem to be affected by age at diagnosis. Therefore, younger patients can be followed-up as their elderly counterparts. However, the clinical decision making should carefully evaluate patient's age, as younger individuals have significantly more time to progress towards malignancy.



P 3. SURVEILLANCE OF THE REMNANT PANCREAS AFTER PARTIAL PANCREATECTOMY FOR IPMN: KYUSHU UNIVERSITY EXPERIENCE

T Ohtsuka, Y Miyasaka, Y Mori, K Nakata, Y Oda, M Nakamura
Kyushu University

Background: One of the revisions in the recently published Fukuoka consensus guidelines for the management of IPMN (Pancreatology, 2017) highlights the need for long-term surveillance for remnant pancreas after partial pancreatectomy for IPMN. Four possibilities may occur in the postoperative remnant pancreas: (1) progression of indolent IPMN left untreated in the remnant pancreas at the time of initial operation; (2) metachronous development of multifocal IPMNs; (3) recurrence of the initially resected IPMN; (4) and metachronous development of concomitant pancreatic ductal adenocarcinoma (PDAC).

Methods: In this study, we retrospectively reviewed our data on 615 IPMN patients.

Results: Progression of untreated indolent IPMN or metachronously developing multifocal IPMN in the remnant pancreas were rarely observed. However, 5- and 10-years cumulative incidences of recurrent IPMN and metachronous PDAC in the remnant pancreas, are 7.8% and 11.8%, respectively; hence, long-term postoperative surveillance is necessary (Ann. Surg, 2016).

The predictors for the recurrent IPMN include: main duct IPMN (MD-IPMN), high grade dysplasia or invasive carcinoma, and tumor location in the distal pancreas at the time of initial operation. In line with this, even with negative surgical margins, the incidence of recurrence of MD-IPMN in the remnant pancreas is still 14%, which may be due the monoclonal skip progression, supported by our previous molecular assessment studies (Surgery, 2015; Ann Surg, 2017). Remnant pancreatectomy for recurrent MD-IPMN provides the same prognosis as that without recurrence, therefore, prophylactic total pancreatectomy is not always necessary at the time of initial operation for MD-IPMN, if surgical margin is negative (Ann Surg, 2014). On the other hand, predictive factors for the metachronous PDAC in the remnant pancreas are the presence of MUC2 negative IPMN (gastric or pancreatobiliary type) or concomitant PDAC at the time of initial operation. However, cumulative incidence of second PDAC in the remnant pancreas after resection of first PDAC concomitant with IPMN is not significantly different from that after resection PDAC without IPMN, indicating that long-term survivors after resection of PDAC are of high risk for second PDAC in the remnant pancreas, irrespective of the presence or absence of IPMN (Surgery, 2018). Although, it is sometimes difficult to discriminate the invasive IPMN from concomitant PDAC, pathological subtype and molecular assessments of resected IPMN using MUC staining and GNA/KRAS mutational analyses strongly aid the differential diagnosis of these two different entities (Pancreas, 2015), and this will contribute to know the principal of the development and progression of IPMN as well as concomitant PDAC, and to support the adequate management of IPMN.

Conclusion: Taken together, our recent efforts strongly support the revised Fukuoka guidelines 2017.

P 4. IDENTIFICATION OF AN OPTIMAL CUT-OFF FOR DRAIN FLUID AMYLASE ON POSTOPERATIVE DAY ONE FOR PREDICTING CLINICALLY-RELEVANT FISTULA AFTER DISTAL PANCREATECTOMY

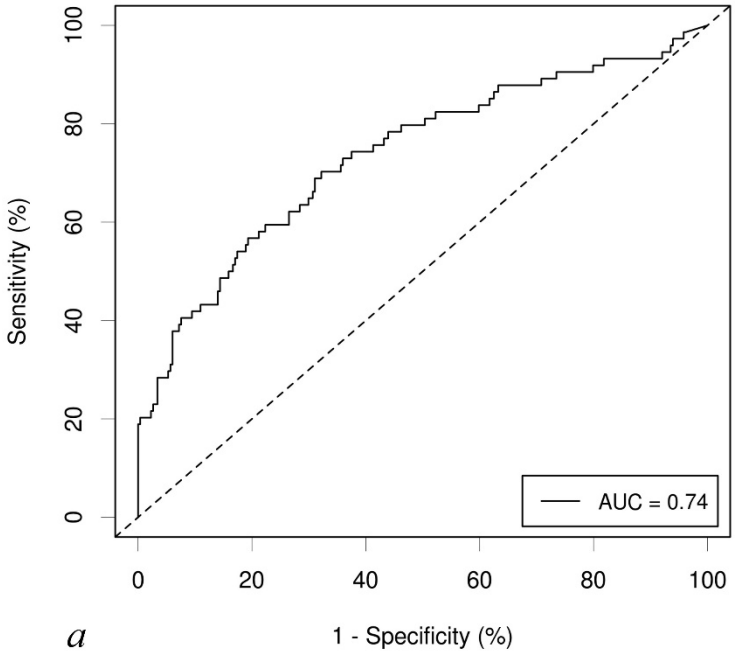
L Maggino, G Malleo, C Bassi, V Allegrini, JD Beane, RM Beckman, B Chen, EJ Dickson, JA Drebin, BL Ecker, DL Fraker, MG House, NB Jamieson, AA Javed, SJ Kowalsky, MK Lee, MT McMillan, RE Roses, R Salvia, V Valero III, LKP Velu, CL Wolfgang, AH Zureikat, CM Vollmer Jr
University of Pennsylvania

Background: Drain fluid amylase value on the first post-operative day (DFA1) is a well-recognized predictor of clinically relevant fistula (CR-POPF) after pancreatoduodenectomy, but its role in distal pancreatectomy (DP) is largely unexplored. The aim of this study was to investigate the relationship between DFA1 and CR-POPF after DP, and to identify the cut-off of DFA1 that optimizes CR-POPF prediction.

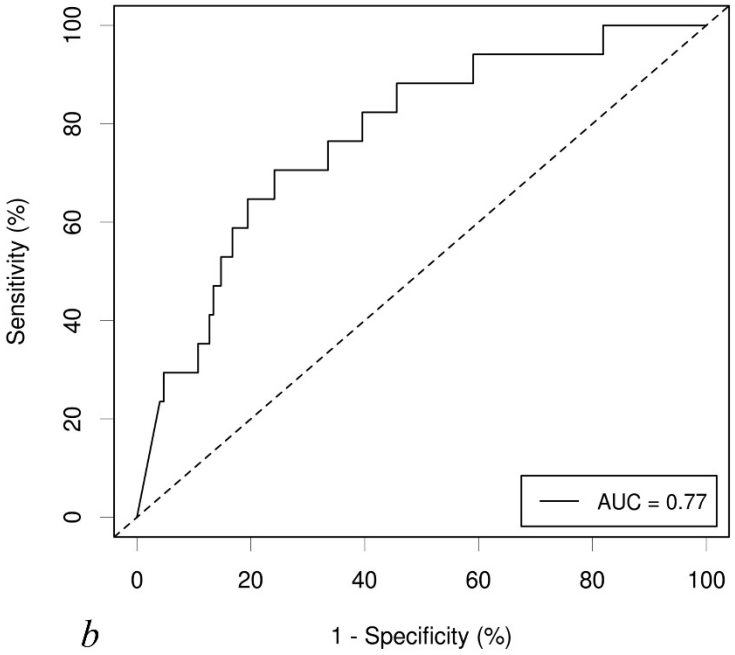
Methods: DFA1 levels were correlated with CR-POPF in two independent multi-institutional sets of DP patients: developmental (n = 338; years 2012-2017) and validation cohort (n = 166; years 2006-2016). Cut-off choice was based on Youden index calculation, and its ability to predict CR-POPF occurrence was tested in a multivariable regression model adjusted for clinical, demographic, operative, and pathological variables.

Results: In the developmental set, median DFA1 was 1745 U/L and the CR-POPF rate was 21.9%. DFA1 correlated with CR-POPF with an area under the curve of 0.737 ($p<0.001$, Table 1a). A DFA1 of 2000 U/L had the highest Youden Index, with 74.3% sensitivity and 62.1% specificity. The CR-POPF rate was significantly higher in patients with DFA1 ≥ 2000 U/L (35.5% versus 10.4%, $p<0.001$). Overall and Fistula Accordion, as well as the Postoperative Morbidity Index (PMI), were strongly associated with the cut-off. Patients with DFA1 ≥ 2000 U/L had both a longer duration of drainage and hospital stay than those with lower amylase values (5 versus 3 days, $p<0.001$ and 8 versus 7 days $p=0.002$, respectively). Patients in the validation cohort displayed different demographic and operative characteristics, lower values of DFA1 (784.5 U/L, $p<0.001$), and reduced CR-POPF rate (10.2% $p<0.001$). In this set, DFA1 correlated with CR-POPF with an area under the curve of 0.776 ($p<0.001$, Table 1b). Notably, a DFA1 of 2000 U/L had the highest Youden Index in this cohort as well, with 64.7% sensitivity and 75.8% specificity. At multivariable analysis, DFA1 ≥ 2000 U/L was the only factor significantly associated with CR-POPF in both cohorts.

Conclusion: A DFA1 of 2000 U/L optimizes CR-POPF prediction after DP. These results provide the substrate to define best practices and improve outcomes after DP, as has been already done with pancreatoduodenectomy. Going forward, the identified cut-off might be employed in the design of a trial of early drain removal in patients receiving DP.


Sensitivity (%)
0
20
40
60
80
100
AUC = 0.74
1 - Specificity (%)

a


Sensitivity (%)
0
20
40
60
80
100
AUC = 0.77
1 - Specificity (%)

b

P 5. PROGNOSTIC ROLE OF THE PARENCHYMAL FROZEN TRANSECTION MARGIN DURING PANCREATICODUODENECTOMY FOR DUCTAL PANCREATIC ADENOCARCINOMA

G Guarneri, S Crippa, D Tamburrino, S Partelli1, G Balzano, C Doglioni, C Rubini, G Zamboni, M Pagnanelli, A Fogliati, G Gasparini, M Falconi
San Raffaele Scientific Institute

Background: During pancreatectomy for ductal adenocarcinoma (PDAC) an intra-operative frozen section analysis of the transection margin is usually performed to achieve an R0 resection. An extension of the resection is required for positive margins until a total pancreatectomy (TP). However, it is unclear whether an extended resection up to TP leads to a survival advantage.
Objective of this study is to evaluate disease-specific (DSS) and disease-free survival (DFS) in patients who underwent TP for PDAC compared to standard or extended pancreaticoduodenectomy (PD).

Methods: Patients with head PDAC were divided into three groups per type of resection: standard PD (SPD), extended PD (EPD) or TP because positive transection margin(s). Patients with IPMN associated PDAC were excluded. Survival analysis as well as evaluation of pathological data and postop morbidity/mortality were performed.

Results: Between 2009 and 2016, 313 patients underwent SPD, 22 EPD group and in 36 TP was performed because of repeated positive margins.
The three groups were homogenous for age, sex, BMI, ASA score and intra-operative variables. No differences were observed among the three groups regarding N+ rate, number of positive nodes and lymph node-ratio, perineural and microvascular invasion. In the TP group a statistically significant increase in peri-operative mortality (O.R. 2.1, IC95% 0.03-0.5, p=0.04) was observed. Moreover, in TP group the rate of R1 resections was significantly higher than in SPD and EPD groups (X^2: 4.52, p=0.033).
Compared to SPD and EPD patients, those who underwent TP had a significant decrease of DFS (median: 11 months in TP, 12 in EPD and 20 in SPD, p=0.002) and DSS (median: 16 months in TP, 17 in EPD and 27 in SPD, p= 0.001).

Conclusion: In patients with head PDAC, TP performed to achieve a negative pancreatic resection margin is still associated with a significant rate of R1 resection (retroperitoneal margin), with higher postoperative mortality and worse both DFS and DSS, when compared to SPD or EPD. Therefore, in this setting, once after PD the transection margin is positive TP does not seem useful.

P 6. QUALITY OF LIFE AFTER PANCREATODUODENECTOMY - 1-YEAR ANALYSIS FROM A GERMAN PROSPECTIVE MULTICENTER TRIAL (RECOPANC)

SV Zemskov, HV Lapshyn, ES Petrova, OV Dronov, T Keck, UF Wellner
Bogomolets National Medical University

Background: While most surgical literature focuses on perioperative complications and survival after pancreatoduodenectomy (PD), studies of quality of life (QoL) remain scarce. Current studies provide only limited investigation on patient and surgery factors that influence QoL before and after the operation. In this study we analyzed the influence of these factors on QoL after PD.

Methods: 320 patients (188 men / 132 women) undergoing PD from 2011 to 2012 in scope of the RECOPANC trial were included. Median age was 68 years, the most frequent indication were periampullary adenocarcinomas (70%, including pancreatic). QoL was measured using the EORTC-QLQ-C30 and PAN26 questionnaires before operation and hospital discharge, as well as 6 and 12 months after operation. Data obtained were processed in accordance to the EORTC scoring manuals. Changes in QoL were tested for influence of putative factors in univariable generalized linear model. Influence of patient's baseline and surgical factors on QoL was categorized as early (present not later than 6 months postoperatively) and late (present at 12 months postoperatively).

Results: Results are represented in Tab.1. Completion pancreatectomy had persistent negative effect on Body image, Digestive symptoms, Role and Physical functioning. Pancreatic fistula negatively influenced Digestive symptoms, Appetite and Weight loss. The mentioned QoL domains were being affected by both factors during at least one year. Extended lymphadenectomy and age over 74 years were not associated with major QoL impairment.

Conclusion: Obtained results may be useful in clinical counseling and prognostication for patients undergoing PD.

Table 1. QoL time trends and factors of influence.

	Body Image	Digestive Symptoms	LIver symtoms	Role Functioning	Taste changes	Constipation	Dyspnea	Appetite loss	Weight loss	Physical Functioning	Emotional Functioning	Fatigue	Muscle Weakness
Age>74						bc	bc						
Sex											b	b	c
PAMPAC			abc										
POPF		abc						bc	bc				
PPH			bc										
CPE	abc	abc		c						ac			
DGE					bc								
LAD							c						

Abbreviations: Abbreviations: a/b/c- significant ($p<0.05$) association at discharge/6 months/12 months after operation by generalized linear model, POPF postoperative pancreatic fistula, PAMPAC periampullary adenocarcinoma, LAD lymphadenectomy, DGE delayed gastric emptying, PPH postoperative pancreatic hemorrhage, CPE completion pancreatectomy

P 7. HEALTH DISPARITIES IMPACT THE EXPECTED TREATMENT OF PANCREATIC DUCTAL ADENOCARCINOMA NATIONALLY

W Lutfi, MS Zenati, AH Zureikat, HJ Zeh, ME Hogg
University of Pittsburgh Medical Center

Background: National adherence to guidelines recommended for treatment of resectable pancreatic ductal adenocarcinoma (PDAC) is a concern. We recently sought to address failure to treat for all PDAC stages using institutional data and found that demographic factors including age and gender were associated with treatment adherence disparities. This study aims to evaluate national expected treatment (ET) adherence for all PDAC stages. We hypothesized that both patient and hospital demographics are associated with national ET disparities for PDAC.

Methods: We evaluated PDAC patients from the National Cancer Data Base (NCDB) from 2004 to 2013 who underwent treatment for clinical stages I through IV. ET was defined as surgery with or without chemotherapy or radiation therapy for stage I and II, chemotherapy or radiation for stage III, and chemotherapy for stage IV. Unexpected treatment (UT) was defined as no surgery for stage I and II, surgery for stage III, and radiation or surgery for stage IV. Patients without any therapy are no treatment (NT).

Results: 171,351 patients were identified. 56,589 (33.0%) were stage I and II, 23,459 (13.7%) were stage III, and 91,0303 (53.3%) were stage IV. 48.4% of patients received ET, 14.7% received UT, and 36.9% received no treatment (stage I and II - ET=41.1%, UT=30.0%, NT=28.9%; stage III - ET=65.4%, UT=6.8%, NT=27.8%; stage IV - ET=48.5%, UT=7.3%, NT=44.2%). On multivariable logistic regression analysis, older age, female sex, non-white race, lower socioeconomic status (SES), being uninsured or having Medicare, higher comorbidity index, being treated at a non-academic center, and being treated at a low volume hospital were all independent negative predictors of receiving ET. Subgroup analysis revealed that high volume academic centers had higher ET adherence for stage I/II and stage IV patients (P<0.001), however there were similar demographic predictors of poor adherence to ET. In terms of survival for stage I and II patients, ET had the best overall survival followed by UT and then NT (P<0.001). For locally advanced stage III, UT had the best overall survival followed by ET and NT (P<0.001). Of the stage III patients that received UT (surgery), 53% received neoadjuvant therapy and 51% had vascular abutment based on NCDB coding. For metastatic stage IV patients, UT had the best overall survival followed by ET and NT (P<0.001). Of the stage IV patients that received UT, 22% underwent surgical resection.

Conclusion: Treatment, especially surgery, improves survival for patients with PDAC. Several patient and hospital factors impacted the ET of pancreas cancer on a national level. These national treatment disparities for PDAC are cause for concern, even at high-volume academic centers where ET adherence is highest. Future studies are needed to identify the causes of treatment disparities for PDAC with intervention measures aimed to relieve treatment disparities.

P 8. TARGETING PARG, A BETTER TARGET THAN PARP1, IN PANCREATIC CANCER

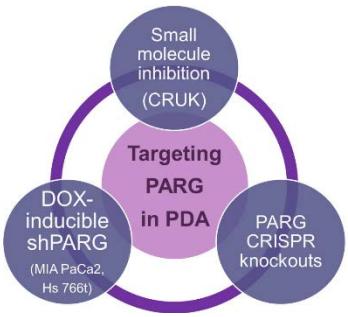
SN Chand, A Ramirez, A Jain, A Nevler, CY Lowder, JA Cozzitorto, DI James, A Jordan, KM Smith, ID Waddell, CJ Yeo, JM Winter, JR Brody
Thomas Jefferson University

Background: Metastatic pancreatic ductal adenocarcinoma (PDA) has an average survival of less than one year. There is a pressing need to identify patient subgroups for treatment with novel targeted agents and the necessity to combat increasing incidence of therapeutic resistance. In a previous study, we identified that poly(ADP) ribose glycohydrolase (PARG) is a critical player in mediating resistance to PARP inhibitor (PARPi); therefore targeting PARG is a strategy to enhance PARPi therapy in PDA and can be optimized to benefit patients with or without homologous repair (HR) deficiencies.

Methods: We developed and characterized multiple PARG inhibition models in both DNA- repair proficient (MIA PaCa-2) and deficient (Hs766t) PDA lines; doxycycline-inducible shPARG knockdown, CRISPR- mediated PARG knockout and small molecule inhibition via a series of potent first-in-class, cell-active PARG inhibitors (PARGi).

Results: Our data show that PARG inhibition is synthetic lethal with DNA damage repair deficiency in PDA cells. This was further validated in isogenic colorectal cell lines with varying DNA repair functionality: DLD1 [BRCA2 (+/+, +/-, -/-)] and RKO [FANCC (+/+, +/-, -/-)]. We have also shown that PARG inhibition enhances PARPi sensitivity through increased accumulation of DNA damage, apoptosis and persistence of detrimental PARylation. Moreover, PARP1 was trapped on the chromatin in response to both PARPi treatment as well as DNA damaging agents such as oxaliplatin. Complementary xenograft experiments were performed wherein MIA.shPARG cells were injected in nude female athymic mice. PARG inhibition by doxycycline induction significantly decreased tumor volumes (50% decrease, p-value 0.0165), which was further enhanced with olaparib treatment (70% decrease, p- value 0.0004), when compared with control arms. Similar results were obtained when DOX-fed mice with MIA.shPARG cells were treated with olaparib at 50mg/kg. Furthermore, in an attempt to mimic and break long-term in vivo PARPi resistance, doxycycline-mediated PARG inhibition was induced in the olaparib treatment arm on day 56 (with established tumors, and exposed to olaparib for 3weeks i.e. 15 injections). This resulted in a significant decrease in tumor volume when compared to control untreated arm (46% decrease, p-value 0.0025) and the olaparib only treatment arm (25% decrease, p-value 0.0124). We are currently validating these results in a DDR-deficient HST.shPARG cell line, as well as with CRISPR knockouts of PARG.

Conclusion: Together these studies validate PARG as a therapeutically relevant and "druggable" target in both HR-proficient and deficient PDA cells, and lays the groundwork to optimize PARPi-based as well as other DNA targeted therapies (e.g. oxaliplatin) in the treatment of PDA.



P 9. DOES NEOADJUVANT THERAPY AFFECT PERIOPERATIVE OUTCOMES IN SARCOPENIC PATIENTS WITH PANCREATIC ADENOCARCINOMA?

DL Kahler, MS Zenati, AJ Klobuka, JJ Tobler, PR Varley, ME Hogg, HJ Zeh, AA Borhani, AH Zureikat
University of Pittsburgh Medical Center

Background: Sarcopenia is thought to adversely affect outcomes of resected pancreatic ductal adenocarcinoma (PDA). Neoadjuvant chemotherapy (NAC) is being increasingly utilized in PDA, however its impact on sarcopenic patients is unknown. This study sought first to determine the impact of NAC on peri-operative outcomes of sarcopenic patients, and second, to determine outcomes of NAC-induced sarcopenia during the neoadjuvant period.

Methods: Retrospective analysis of resected PDA patients between 2011-2016. Sarcopenia was defined as the lower quartile of average psoas density as evaluated by cross-sectional CT scan at L3. NAC-induced sarcopenia was defined as change from baseline of >5% in average psoas density from the baseline scan compared to post treatment (preoperative) scan. To assess the impact of NAC on sarcopenic patients, multivariable models were generated with mortality, major complications, length of hospital stay, readmission, and discharge disposition (home versus skilled facility) as the primary outcome.

Results: Of 204 evaluable patients, 120 (59%) received NAC, and 51 were sarcopenic at baseline. Average age was 67, and 48.5% were female. On multivariate analysis, NAC did not impact complications, length of hospital stay, readmissions, or discharge disposition in sarcopenic patients. Within the NAC cohort, 35 (29%) exhibited development of advancing sarcopenia during NAC therapy. No differences were observed in perioperative outcomes of patients who developed sarcopenia as a consequence of NAC compared to those who did not.

Conclusion: These data suggest that for pancreatic cancer, NAC does not impact the outcomes of patients with baseline sarcopenia or those that develop evidence of sarcopenia during neoadjuvant treatment. NAC should therefore not be withheld in sarcopenic patients with pancreatic ductal adenocarcinoma.

P 10. THE IMPACT OF FAILURE TO ACHIEVE SYMPTOM CONTROL AFTER RESECTION OF FUNCTIONAL NEUROENDOCRINE TUMORS: AN 8-INSTITUTION STUDY FROM THE US NEUROENDOCRINE TUMOR STUDY GROUP

MY Zaidi, AG Lopez-Aguiar, GA Poultsides, E Makris, M Dillhoff, EW Beal, FG Rocha, ZS Kanji, K Idrees, P Marincola Smith, H Nathan, M Beems, ER Winslow, JR Barrett, RC Fields, BA Krasnick, K Cardona, SK Maithel
Emory University

Background: The goals of resection for patients with functional neuroendocrine tumors (F-NETs) are two-fold: oncologic benefit and symptom control. The interaction between the two, however, is not well understood.

Methods: All patients with F-NETs of the pancreas, liver, duodenum, and ampulla who underwent curative-intent resection between 2000 and 2016 were identified. Cox regression analysis was utilized to determine clinicopathologic factors associated with reduced recurrence-free survival (RFS). A multivariable model was created by incorporating all variables associated with RFS with $p<0.1$.

Results: Of 260 patients with resected F-NETs, 230 underwent curative-intent resection. 53% were insulinomas, 35% gastrinomas, and 12% other. 21% had a known genetic syndrome (majority MEN-1), 23% had LN positive disease, 80% underwent an R0 resection, and 14% had no postoperative symptom improvement (SI). Patients who did have SI were more likely to have an insulinoma ($p=.01$), no genetic syndrome ($p=.001$), and an R0 resection ($p=.007$). LN positive disease did not correlate with postoperative SI. Factors associated with reduced RFS included non-insulinoma histology, known genetic syndrome, LN positive disease, R1 margin, and lack of SI. On MV analysis, only the failure to achieve SI following resection persisted as being associated with reduced RFS (Table). Considering only those patients with an R0 resection, failure to achieve SI was still associated with worse 3-yr RFS compared to patients with SI (36% vs 80%; $p=0.006$).

Conclusion: Failure to achieve symptomatic improvement after resection of functional NETs is associated with worse recurrence-free survival, even when accounting for histologic type, presence of genetic syndromes, R1 resection margin, and LN involvement. These patients may benefit from short-interval periodic imaging postoperatively to assess for earlier radiographic recurrence of disease.

Association Between Clinicopathologic Variables and Decreased Recurrence-Free Survival

	Univariable			Multivariable		
Variable	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Type of Functional Tumor						
Insulinoma	Ref	--	--	Ref	--	--
Gastrinoma	2.8	(1.3-6.1)	0.006	1.1	(0.6-2.0)	0.75
Other (including glucagonoma, somatostatinoma, VIPoma)	2.7	(1.0-7.2)	0.042	--	--	--
Known Genetic Syndrome	1.8	(0.9-3.5)	0.077	0.68	(0.2-2.0)	0.49
Lymph Node Positive	1.8	(0.9-3.6)	0.080	1.6	(0.6-4.6)	0.35
R1 Resection Margin	2	(1.0-3.9)	0.052	0.45	(0.1-1.8)	0.25
Failure of Symptom Improvement	**3.1**	**(1.3-7.2)**	**0.008**	**4.7**	**(1.3-16.6)**	**0.016**

P 11. CLINICAL IMPLICATIONS OF INTRAOPERATIVE FLUID THERAPY IN PANCREATIC SURGERY: IT IS NOT JUST WATER

S Andrianello, G Marchegiani, E Bannone, G Masini, G Malleo, GL Montemezzi, E Polati, C Bassi, R Salvia
Verona University

Background: Recent studies have suggested that intraoperative fluid overload is associated with a worse outcome after major abdominal surgery. However, evidence in the field of pancreatic surgery is still not consistent. The aim of this study was to evaluate whether intraoperative fluid management could affect the outcome of a major pancreatic resection.

Methods: Prospective analysis of 350 major pancreatic resections performed in 2016 at the Department of General and Pancreatic Surgery €“ The Pancreas Institute, University of Verona Hospital Trust. Patients were dichotomized according to intraoperative fluid volume administration into near-zero fluid balance (NZF €“ infusion rate 3 mL/kg/h) and liberal fluid balance groups (LF - >3 mL/kg/h). Intraoperative fluid administration was then correlated to the postoperative outcome.

Results: Overall, a LF balance was associated with an increased rate of Clavien-Dindo IIIB (50.5% vs. 34.5%; p=0.02) and delayed gastric emptying (DGE) (8.8% vs. 1.8%; p=0.05). A NZF balance was associated with a reduced incidence of biliary fistula (0% vs. 7.9%; p=0.05) and DGE (5% vs. 11.6%; p=0,04) but an increased rate of post-operative acute pancreatitis (75% vs. 49.2%; p=0.02) after pancreaticoduodenectomy. Considering patients with a soft pancreatic remnant, a NZF balance was associated with an increased rate of pancreatic fistula (60% vs. 45.2%, p= 0.02).

Conclusion: Considering all pancreatic resections, a LF balance is associated with an increased rate of postoperative morbidity. However, in the case of PD with a soft pancreas, a NZF balance could lead to pancreatic stump ischemia and anastomotic failure. Intraoperative fluid management should be managed according to patient's pancreas-specific risk factors.

Table 2 - *Post-operative outcomes of all major pancreatic resections stratified by intraoperative fluid regimens*					
		Overall (n=350)	LF (n= 295)	NZF (n= 55)	p
Overall morbidity		241 (68.9%)	199 (67.5%)	42 (76.4%)	0.2
Surgical morbidity		180 (51.4%)	146 (49.5%)	34 (61.8%)	0.1
Abdominal abscess		112 (32%)	93 (31.5%)	19 (34.5%)	0.6
PPH		31 (8.9%)	27 (9.2%)	4 (7.3%)	0.4
PPH grade	A	6 (1.7%)	5 (1.7%)	1 (1.8%)	0.4
	B	13 (3.7%)	11 (3.7%)	2 (3.6%)	
	C	12 (3.4%)	11 (3.7%)	1 (1.8%)	
DGE		27 (7.7%)	26 (8.8%)	1 (1.8%)	0.05
DGE grade	A	4 (1.1%)	4 (1.3%)	0	0.4
	B	10 (2.9%)	9 (3%)	1 (1.8%)	
	C	13 (3.7%)	13 (4.4%)	0	
Sepsis		34 (10%)	31 (10.8%)	3 (5.5%)	0.1
Relaparotomy		33 (9.4%)	28 (9.5%)	5 (9.1%)	0.5
ICU stay		39 (11.1%)	33 (11.2%)	6 (10.9%)	0.5
LHS (median, range)		9 (5 – 371)	9 (5 – 371)	10 (6 – 75)	0.8
Mortality (in-hospital)		11 (3.1%)	11 (3.7%)	0	0.2
Readmission (30-days)		15 (4.3%)	13 (4.4%)	2 (3.6%)	0.5
Clavien-Dindo ≥ IIIB		168 (48%)	149 (50.5%)	19 (34.5%)	0.02

P 12. TRAVEL DISTANCE AFFECTS RATES AND REASONS FOR READMISSION AFTER PANCREATECTOMY

RE Simpson, CY Wang, MG House, NJ Zyromski, CM Schmidt, A Nakeeb, EP Ceppa
Indiana Univesity

Background: Complex surgical care is often centralized to high volume institutions, leading to increased travel distances for patients. We sought to determine if increased travel distance to the index hospital altered readmission rates following pancreatectomy.

Methods: Pancreatectomies from 2013-2016 were retrospectively reviewed from a single high-volume institution. Travel distance for 947 patients was determined using Google Maps; patients were grouped by distance of <50 vs. 50-100 vs. >100miles. Visits (Observation or Readmission) and corresponding reasons were gathered through review of medical records.

Results: 222 patients (23%) had a Visit to any hospital (AH) within 90 days postoperative; 195 (88%) were to the index hospital (IH). The <50miles group had the highest Visit rate to AH (28% vs. 18% vs. 25%; p-value 0.01) and the IH (26% vs. 15% vs. 21%; p-value 0.003) when compared to 50-100 and >100miles. This trend was similar for Observations alone. The Readmission rate between groups did not differ. Gastrointestinal (GI) complaints (failure to thrive, pain, nausea) as the sole reason led to 46 of the 222 patients requiring Visits to AH at 90-days (20.7%.) This was highest in <50miles group, which was statistically significant for all Visits and Observations alone at AH and the IH. Demographics, perioperative variables, mortality, and major morbidity including clinically significant pancreatic fistula (POPF) were similar between groups.

Conclusion: Patients living closest to the IH had the highest Visit rate following pancreatectomy and Observation rate without affecting Readmission rate. Proximity to the hospital and GI complaints were the driving factors for repeat hospitalization without readmission. Improved inpatient education and outpatient symptom management may reduce repeat hospitalization.

Distance Group (Miles)	N	Length of Stay	90-Day Visit Rate AH (IH)	90-Day Admit Rate AH (IH)	90-Day Obs Rate AH (IH)	30-Day Morbidity	30-Day Mortality	Grade B+C POPF	90-Day GI Visit Rate AH(IH)	90-Day GI Admit Rate AH(IH)	90-Day GI Obs Rate AH(IH)
<50	300	7(1-82)	28%* (26%*)	23% (22%)	6%* (6%*)	112 (37%)	9 (3%)	32 (11%)	7%* (7%*)	4% (4%)	4%* (4%*)
50-100	300	7(2-175)	18% (15%)	17% (15%)	2% (1%)	117 (39%)	3 (1%)	27 (9%)	3% (3%)	2% (2%)	0.3% (0.3%)
>100	347	7(1-79)	25% (21%)	22% (18%)	3% (3%)	124 (36%)	5 (1%)	28 (8%)	5% (4%)	4% (2%)	1% (1%)
*rate showed statistically significant difference based on distance group, p<0.05											
Admit=readmissions, Obs=observations, Visit=readmissions and/or observations, POPF=postoperative pancreatic fistula											

P 13. CIRCULATING NEUROENDOCRINE GENE TRANSCRIPTS (NETEST) DECREASE EARLY AFTER RADICAL PANCREATIC SURGERY: PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

S Partelli, M Kidd, F Muffatti, V Andreasi, F Giannone, I Modlin, M Falconi
San Raffaele Scientific Institute

Background: Specific biomarkers for predicting response and risk of recurrence after surgery for pancreatic neuroendocrine tumors (PanNET) are still lacking. Aim of this prospective study was to evaluate if blood measurement of neuroendocrine gene transcripts (NETest) correlates with the efficacy of surgical resection for PanNET

Methods: Between April and November 2017, all patients affected by PanNETs scheduled for surgery were enrolled in this prospective study (NCT 03012789). Whole blood samples for NETest and plasma for Chromogranin A (CgA) were collected preoperatively and on postoperative day 1 (POD1) and 5 (POD5). Transcripts were blinding measured by real-time quantitative reverse transcription PCR (qRT-PCR) and multianalyte algorithmic analysis (NETest); CgA by enzyme-linked immunosorbent assay (ELISA).

Results: Fourteen patients underwent R0 surgical resection for PanNET. NETest score was increased in all 14 patients preoperatively with a median of 73% (IQR 40;93%). In 8 patients, a high disease activity was found (NETest score > 47%). The median NETest score was 40% (IQR 27;80%) and 27% (IQR 27;35%) in POD1 and POD5. NETest levels were significantly lower compared to preoperative values in both POD1 (P=0.009) and POD5 (P<0.0001), respectively. The median preoperatively CgA value was 38µg/l (IQR 18;38µg/l) and it was elevated in 2 patients (cut-off:150µg/l). The median preoperative CgA value was similar to POD1 median CgA value (37.8µg/l) and POD5 median CgA value (60.4µg/l) (P>0.05).

Conclusion: NETest decreases significantly after radical resection for PanNET suggesting that it is a promising biomarker for early definition of surgical efficacy.

P 14. PREDICTING POST-SURGICAL SURVIVAL IN PANCREATIC ADENOCARCINOMA USING A TUMOR SOLUBLE PROTEIN SIGNATURE

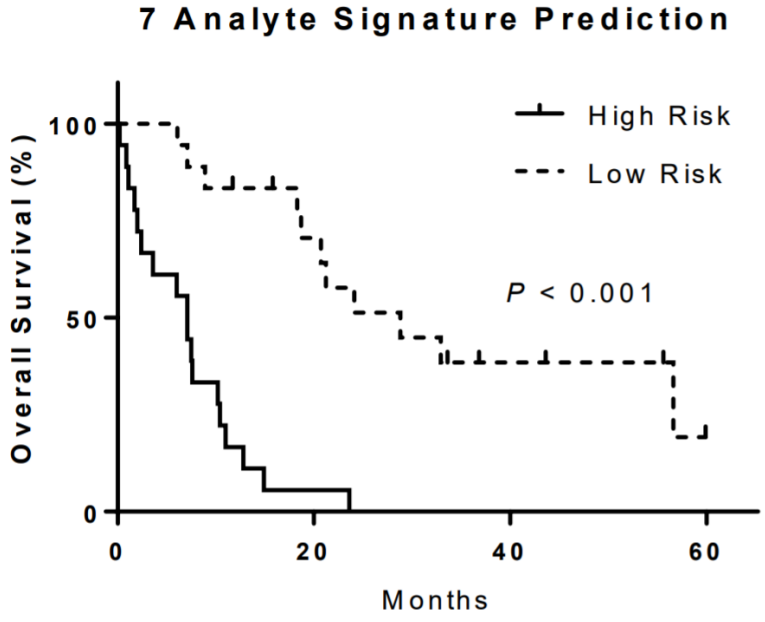
MH Gerber, W Gooding, D Delitto, JL Cioffi, BB DiVita, SM Wallet, JG Trevino, SJ Hughes
University of Florida

Background: Overall survival in resectable pancreatic cancer is poor, and we are unable to predict which patients will have long term survival benefits after surgery. We hypothesize that a soluble immunological protein signature from the tumor microenvironment can predict survival in patients with pancreatic adenocarcinoma.

Methods: Tissue lysates from resected surgical specimens of pancreatic ductal adenocarcinoma (n=36) were analyzed for concentrations of 36 cytokines, chemokines, and growth factors. Uniquely informative analytes were discovered using a logistic regression analysis. A covariate penalized logistic model using the identified analytes was created. The overall survival was plotted using Kaplan-Meier survival curves which were then analyzed using the log-rank test.

Results: Analysis of the 36 analytes identified 7 informative analytes that were used in the survival algorithm. The prediction values generated by algorithm for each tissue sample were split using the median into high risk and low risk groups. The two groups consisted of 18 patients each, and the median overall survival in the high risk group was 7 months compared to a median overall survival in the low risk group of 29 months (P-value <0.001) (see figure). The only clinical parameter associated with survival was the positive lymph node ratio (HR 2.2; P-value <0.01). In a proportional hazards regression, the 7 analyte signature was independently associated with survival when conditioned to the lymph node ratio (P-value < 0.001).

Conclusion: A soluble protein signature from the tumor microenvironment may predict long term survival post-surgery in pancreatic adenocarcinoma. The protein signature has prognostic ability independent from the positive lymph node ratio. This finding raises the potential for the use of protein signatures for a precision approach to patients with pancreatic cancer.



P 15. MTH1 AS PHENOTYPIC LETHAL TARGET IN PANCREATIC CANCER

MC Hernandez, L Yang, JL Leiting, JR Bergquist, U Warpman Berglund, T Helleday, MJ Truty
Mayo Clinic Rochester

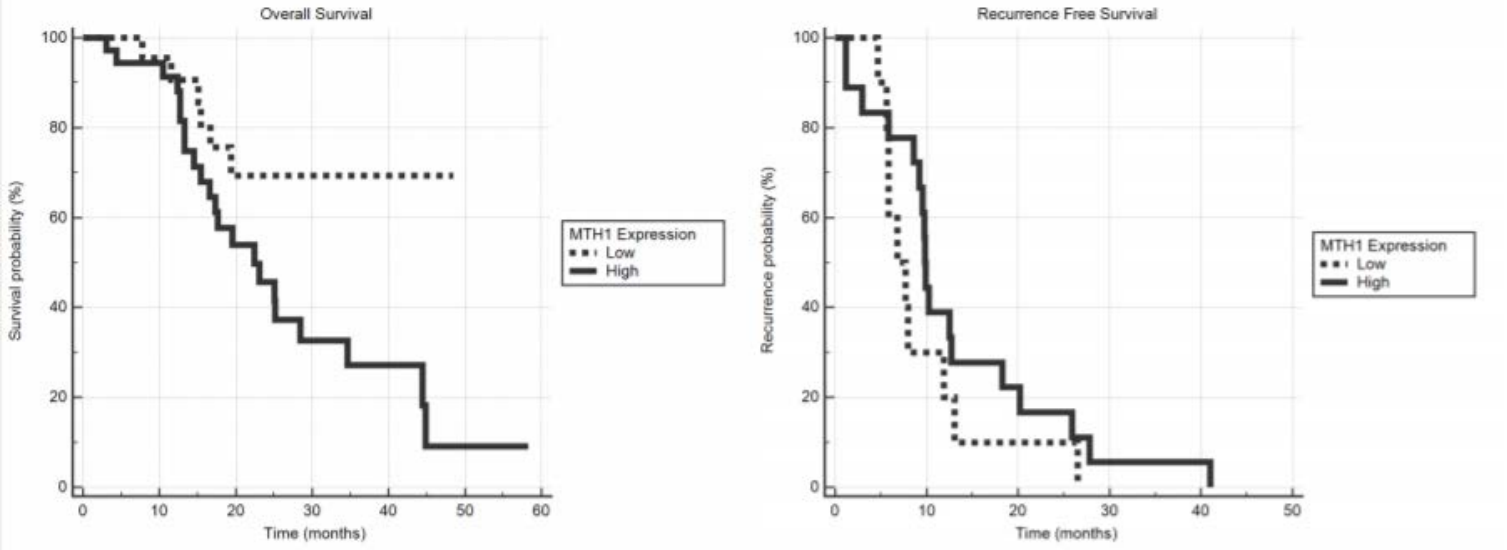
Background: Chemoresistance and development of metastases are hallmarks of pancreatic cancer (PDAC)and portends poor clinical outcomes. PDAC is characterized by a fibrotic hypoxic environment that increases cellular oxidative stress. An antioxidant enzyme, MTH1, is upregulated in several cancers and increased MTH1 activity is required to avoid incorporation of oxidized dNTPs. Novel MTH1 inhibitors (phenotypic lethal) take advantage of non-oncogene addiction concept for anticancer treatment. We utilized an immunohistochemistry (IHC) screen to ascertain the functional MTH1 status of both patient and patient-derived xenograft (PDX) PDAC tissue hypothesizing that (1) patients with high MTH1 expression would demonstrate worse overall survival and (2) that MTH1 expression would correlate with novel MTH1 enzyme inhibitor sensitivity.

Methods: With informed consent and institutional approval, a prospective gastrointestinal malignancy PDX catalog and clinical database is maintained. During 2013-2017, patients with pathologically confirmed PDAC (untreated or neoadjuvant) were implanted into immunodeficient mice from surgically resected cancerous tissue. Patient/PDX MTH1 enzyme status was assessed using IHC and immunoblot. PDAC tissue from engrafted PDX models was digested; cells were seeded onto 96 well plates and cultured in complete media. Increasing concentrations of a novel MTH1 inhibitor were administered. Cell viability of treated cells was normalized to controls. Kaplan-Meier survival analysis with hazard ratios and 95% confidence intervals were determined.

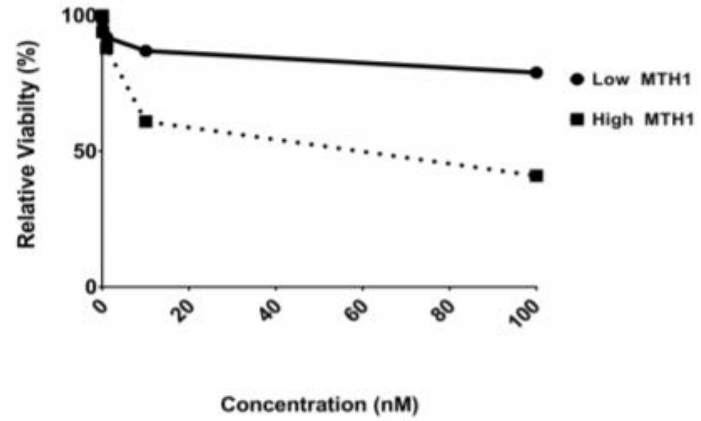
Results: For this study 62 successful PDX engraftments (untreated n=24 and neoadjuvant n=38) were assessed. IHC for MTH1 enzyme demonstrated variable expression in patients untreated or receiving neoadjuvant therapy. Kaplan-Meier analysis demonstrated reduced survival in patients with high MTH1 status (2,3+) compared to low (0,1+) despite treatment status, Figure. In patients with high MTH1 expression, median survival time was diminished compared to low expressers, 26.7 [20.7-32.1] vs 38 [31-45] months, p=0.01. Patients with high MTH1 expression demonstrated a hazard ratio of 2.9 95%CI (1.3-6.1). In selected models, MTH1 inhibition correlated well with degree of expression. PDX models with high expression demonstrated sensitivity to inhibition whereas cells derived from models with low expression resulted in increased cellular viability.

Conclusion: PDAC represents a lethal cancer type with few treatment options for patients with chemoresistant or metastatic disease. We revealed that patients with high MTH1 expression were associated with diminished overall survival compared to those with low MTH1 expression. In several PDAC models (untreated and neoadjuvant) we demonstrate that MTH1 expression appears to correlate with sensitivity to a novel inhibitor. These data will be utilized to enrich for an in vivo trial with this MTH1 inhibitor.

High MTH1 Expression Is Associated with Overall Survival



Increasing MTH1 Inhibitor Decreases Cell Viability in High Expresser



P 16. PREOPERATIVE OPIOID USE ASSOCIATED WITH INCREASED LENGTH OF STAY AFTER PANCREATICODUODENECTOMY

CA Thiels, JR Bergquist, A Habermann, TE Grotz, SP Cleary, RL Smoot, ML Kendrick, DM Nagorney, MJ Truty
Mayo Clinic Rochester

Background: Preoperative opioid use in patients undergoing low complexity operations is associated with increased complications, but its relationship to procedures of greater complexity is unclear. We aimed to assess this impact on outcomes following pancreaticoduodenectomy (PD).

Methods: A single institution, retrospective cohort of adults undergoing elective PD for cancer (1/2009-9/2015). Preoperative users were defined as patients taking opioids 90 days preoperatively. Discharge prescriptions were converted into Oral Morphine Equivalents (OME) and ten-point pain scores were abstracted. Univariate and multivariable analyses compared outcomes of naïve and preoperative users overall and for laparoscopic vs open surgery.

Results: Of 661 PD patients, 131 (19.8%) were preoperative users (Table). These patients had greater mean pain scores over the first three days after surgery (3.4±1.6, vs 2.8±1.4, p<0.001), max pain (7.9±1.9 vs 7.2±2.0, p<0.001), and discharge pain (2.3±1.9 vs 1.8±1.6, p=0.01) than naÃ¯ve patients. The median OME prescribed was 300 (IQR 150,450) with preoperative users receiving more opioids at discharge (mean 496±764 vs 320±489 OME, p=0.03). Thirty-day refill rates were 12.6% (19.1% preoperative vs 10.9% naÃ¯ve, p=0.02). Open and laparoscopic (n=261) PD had similar mean pain scores over the first three days (p=0.51), max pain score (p=0.11) and OME prescribed (p=0.50), but laparoscopic cases had slightly lower pain scores at discharge (1.7±1.6) vs open (1.9±1.7, p<0.01). After controlling for tumor type, texture, and duct size, naÃ¯ve patients had similar odds of ISGPS grade B/C leak (OR 1.13, p=0.68) and delayed gastric emptying (OR 1.05, p=0.87). After controlling for age and complications, preoperative opioid use was associated with increased odds of LOS ≥9 days (OR 1.59, p=0.04).

Conclusion: Following PD, preoperative users had worse pain scores, received more opioids at discharge, refilled prescriptions more frequently, and were more likely to have prolonged LOS. As most opioid utilization research has been focused on low complexity surgery, additional work aimed at optimizing opioid use in complex oncologic operations is warranted.

Table. Univariate comparison of opioid naïve patients to preoperative opioids users.

	All PD Patients n=661	Opioid Naïve Patients n=530	Preoperative Opioid Users n=131	P-value
Female	285 (43.1%)	224 (42.3%)	61 (46.6%)	0.38
Age, in years				**0.03**
<56	131 (19.8%)	98 (18.5%)	33 (25.2%)	
56-64	180 (27.2%)	136 (25.7%)	44 (33.6%)	
65-72	168 (25.4%)	140 (26.4%)	28 (21.4%)	
73-91	182 (27.5%)	156 (29.4%)	26 (19.8%)	
Estimated Blood Loss, in mL				0.67
≤400	299 (45.2%)	245 (46.2%)	54 (41.2%)	
401-700	152 (23.0%)	117 (22.1%)	35 (26.7%)	
701-1,000	104 (15.7%)	83 (15.7%)	21 (16.0%)	
>1,000	106 (16.0%)	85 (16.0%)	21 (16.0%)	
Diagnosis Group				**<0.001**
PDAC	352 (53.3%)	259 (48.9%)	93 (71.0%)	
Other Neoplasm	309 (46.7%)	271 (51.1%)	38 (29.0%)	
Pancreatic Duct Diameter (mm)				0.38
≥5	188 (28.4%)	156 (29.4%)	32 (24.4%)	
4.0-4.9	136 (20.6%)	104 (19.6%)	32 (24.4%)	
3.0-3.9	164 (24.8%)	127 (24.0%)	37 (28.2%)	
2.0-2.9	128 (19.4%)	104 (19.6%)	24 (18.3%)	
≤1	45 (6.8%)	39 (7.4%)	6 (4.6%)	
Gland Texture				**0.02**
Firm	386 (58.4%)	298 (56.2%)	88 (67.2%)	
Soft	275 (41.6%)	232 (43.8%)	43 (32.8%)	
POPF (grade B/C)	130 (19.7%)	108 (20.4%)	22 (16.8%)	0.39
Clinically Significant DGE	114 (17.2%)	92 (17.4%)	22 (16.8%)	1.00
Post-op Hemorrhage	44 (6.7%)	39 (7.4%)	5 (3.8%)	0.17
LOS, median (IQR) in days	8 (6,13)	8 (6, 13)	9 (6, 13)	0.84
LOS ≥ 9 days	308 (46.6%)	241 (45.5%)	67 (51.2%)	0.28
OME Prescribed at Discharge, median (IQR)	300 (150,450)	300 (150, 390)	300 (200, 470)	**0.03**
Refill Rate	83 (12.6%)	58 (10.9%)	25 (19.1%)	**0.02**

DGE, Delayed Gastric Emptying; IQR, Inter-Quartile Range; LOS, Length of Stay; PD, Pancreaticoduodenectomy; PDAC, Pancreatic Ductal Adenocarcinoma; POPF, Post-operative Pancreatic Fistula.

P 17. PREDICTORS OF ROBOTIC PANCREATICODUODENECTOMY PERFORMANCE WITHIN A NOVEL ROBOTIC TRAINING CURRICULUM

LM Knab, MS Zenati, M Rice, A Al-abbas, A Hamad, AH Zureikat, HJ Zeh, ME Hogg
University of Pittsburgh Medical Center

Background: Overcoming a learning curve is necessary for dissemination of the robotic pancreaticoduodenectomy (RPD). As a group, fellows improve performance after completing a robotic simulation curriculum including virtual reality and inanimate biotissue (BT). For the BT curriculum analyzed as a group, the performance parameters of errors, Objective Structured Assessment of Technical Skill (OSATS), and time significantly improved. The relationship between the BT curriculum and fellow operative performance has not been analyzed. We analyzed fellows individually to determine if BT performance is related to robotic operative performance.

Methods: We studied BT drills including 3 anastomoses: hepaticojejunostomy (HJ), pancreaticojejunostomy (PJ), and gastrojejunostomy (GJ). Fellows were scored according to total time spent, frequency, and mastery. Mastery was evaluated by scoring each drill using performance parameters: time to complete the drill, errors, and OSATS (medians). Total parameters were calculated by summing the median scores for each anastomosis for a given parameter. Best scores were defined as the highest OSATS score, and lowest error and completion time. Fellow operative performance was evaluated by determining the percentage of robotic RPD in which the fellow performed the entire resection (steps 1-3). Spearman correlation was used to determine the relationship between BT scores including total number/time as well as individual parameters with fellow operative performance.

Results: Twenty-four fellows operated at the console during RPD and 67% of fellows completed the entire resection. Of 230 RPD logged by fellows who performed BT, 30% of resections were done by fellows. The median number of BT drills performed was 17.5 (IQR=10) and median time spent doing drills was 774 min (IQR=468). A significant correlation was found between RPD resections and both number of anastomoses (P=0.56, p=0.02) and total time spent on the BT anastomoses (P=0.47, p=0.049). Median total errors was inversely correlated with RPD resections performed (rho=-0.62, p=0.007) and median total OSATS was positively correlated with RPD resections (P=0.48, p=0.04). When drills were analyzed individually, HJ errors had the strongest inverse correlation with RPD resections performed (P=-0.80, p=0.0001), and there was a positive correlation between GJ OSATS and RPD resections (P=0.48, p=0.04). For best scores, PJ and HJ errors had a significant inverse correlation with RPD resections (P=-0.5, p=0.03 and P=-0.64, p=0.004, respectively).

Conclusion: The number of BT drills and time spent in deliberate practice is related to operative performance. Individual BT performance parameters, particularly errors, correlate with RPD resections completed by fellows in the operating room. Performing BT drills to minimize errors and maximize OSATS may be a critical step to decreasing the learning curve for the RPD.

P 18. PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) AS NEOADJUVANT THERAPY FOR RESECTABLE OR POTENTIALLY RESECTABLE PANCREATIC NEUROENDOCRINE TUMORS

S Partelli, E Bertani, M Bartolomei, C Perali , F Muffatti, CM Grana, M Schiavo Lena, C Doglioni, S Crippa, N Fazio, G Zamboni, M Falconi

San Raffaele Scientific Institute

Background: Peptide receptor radionuclide therapy (PRRT) is a valid therapeutic option for pancreatic neuroendocrine tumors. The aim of this study was to describe an initial experience with the use of PRRT as a neoadjuvant agent for resectable or potentially resectable pancreatic neuroendocrine tumors (PanNETs).

Methods: The postoperative outcomes of 23 patients with resectable or potentially resectable PanNETs at high risk of recurrence who underwent neoadjuvant PRRT (PRRT group) were compared with 23 patients who underwent upfront surgical operation (upfront surgery group). Patients were matched for tumor size, grade, and stage. Median follow up was 61 months.

Results: The size (median greatest width) of the primary PanNET decreased after neoadjuvant PRRT (59 to 50 mm; P=0.047). There were no differences in intraoperative and postoperative outcomes and there were no operative deaths, but the risk of developing a pancreatic fistula tended to be less in the PRRT group when compared to the upfront surgery group (0/23 vs 4/23; p< 0.02). The incidence of nodal metastases at the time of resection was also less in the PRRT group (n=9/23 vs 17/23; p<0.02). Neither median disease-specific survival (not reached in both groups; p=0.411) nor progression-free survival (52 vs 37 months; p>0.2) differed between groups, but progression-free survival in the 31 patients who had an R0 resection appeared to be greater in the 15 patients in the PRRT group versus 16 patients in the upfront group (median PFS not reached vs 36 months; p<0.05)

Conclusion: Neoadjuvant PRRT for resectable or potentially resectable PanNETs in patients with high-risk features of recurrence appears to be beneficial, but well-designed much larger prospective trials are needed to confirm the safety and the oncologic value of this approach.

P 19. NEOADJUVANT THERAPY OFFERS LONGER SURVIVAL THAN UPFRONT SURGERY FOR POORLY DIFFERENTIATED AND HIGHER STAGE PANCREATIC CANCER

A Nurmi, H Mustonen, H Parviainen, K Peltola, C Haglund, H Seppänen
University of Helsinki

Background: Neoadjuvant therapy for pancreatic cancer remains controversial in terms of patient selection. Our aim was to compare survival and disease recurrence between patients treated with neoadjuvant therapy and subsequent surgery and patients undergoing upfront surgery.

Methods: Out of 399 consecutive pancreatic ductal adenocarcinoma (PDAC) patients operated at Helsinki University Hospital in 2000 to 2015, 75 borderline resectable patients received neoadjuvant therapy and underwent subsequent surgery. Resectable propensity scored patients (n=150) underwent upfront surgery. Neoadjuvant therapy consisted of a combination therapy of folinic acid, fluorouracil, irinotecan and oxaliplatin (Folfirinox), single gemcitabine (Gemzar) or combined with cisplatin (Platinol), nab-paclitaxel (Abraxane) or capecitabine (Xeloda) with or without radiation. Survival was calculated with Kaplan-Meier and compared with the Breslow test. Survival was determined from the first day of treatment for patients receiving neoadjuvant therapy and the day of surgery for others, to death due to pancreatic cancer in disease-specific survival (DSS) and disease progression first recorded in disease-free survival (DFS).

Results: Between 2000 and 2015 median DSS [34 (95% CI 29-39) vs. 26 (20-32) months, p=0.016] and DFS [22 (17-27) vs. 13 (9-17) months, p=0.001] were longer in patients treated with neoadjuvant therapy than in those undergoing upfront surgery. Survival differences were not significant between the groups in the 2000s but were, in turn, among patients treated in the 2010s with better survival for patients treated with neoadjuvant therapy [DSS 35 (25-44) vs. 26 (20-31) months, p=0.008 and DFS 25 (13-36) vs. 13 (6-21) months, p=0.001]. Especially patients with poorly differentiated G3 tumours [DSS 30 (17-42) vs. 11 (8-15) months, p=0.004 and DFS 21 (11-31) vs. 7 (5-8) months, p=0.001] survived three times longer when treated with neoadjuvant therapy. Also, patients with higher stage IIB-III had longer survival when treated with neoadjuvant therapy [DSS 34 (29-40) vs. 20 (14-26) months, p=0.006 and DFS 21 (12-29) vs. 10 (7-13) months, p=0.001].

Conclusion: Patients treated with neoadjuvant therapy had significantly longer survival than those undergoing upfront surgery. Neoadjuvant therapy benefits especially borderline resectable patients with higher stage and poorly differentiated G3 tumours.

P 20. APRATOXIN S10 IS A NOVEL THERAPEUTIC DRUG FOR PANCREATIC DUCTAL ADENOCARCINOMA TREATMENT

MH Gerber, ME Cameron, W Cai, SJ Hughes, H Luesch, JG Trevino
University of Florida

Background: Pancreatic ductal adenocarcinoma (PDAC) is resistant to most chemotherapies. Apratoxins are a novel class of protein translocation inhibitors that can target active secretory pathways critical for PDAC tumor growth. We hypothesized that Apratoxin S10 can inhibit growth of PDAC tumors.

Methods: Patient derived xenografts (PDX) were established at the time of patient surgical resection. The PDX tumors were expanded by orthotopic implantation. Mice were randomized and treated with Apratoxin S10 (0.25 mg/kg) or DMSO as a control by intraperitoneal injections every other day. Tumor sizes were measured using an ultrasound device. Drug concentrations were determined by liquid chromatography tandem mass spectrometry. Tumors were embedded in paraffin and stained for apoptotic and proliferative markers.

Results: Apratoxin S10 concentrates at high levels in the pancreas and salivary glands at 15 minutes and remains significantly higher compared to blood, lung, liver, spleen, brain, and kidney at 48 hours (p-value <0.01). Mice began treatment at 5 weeks post implantation with 10 mice in each group. By day 34, mice receiving treatment had significantly less tumor volume compared to control (161 mm3 vs 314 mm3; p-value <0.001) and overall growth curves were significantly different by treatment at day 34 (p-value <0.001). The final tumor weight was less with Apratoxin S10 treatment (656 mg vs 851 mg; p-value = 0.039) however tumor free body weight was not significantly different (19.3 g vs 19.8 g; p-value = 0.511). The final tumor volume measured ex vivo with calipers was significantly less with Apratoxin S10 treatment (546 mm3 vs 728 mm3; p-value = 0.018). A TUNEL stain for apoptosis yielded no difference between Apratoxin S10 treatment and control (39.8/hpf vs 42.0/hpf; p-value = 0.707). Staining for the proliferation marker, Ki-67, showed a decrease in proliferation in the tumors treated with Apratoxin S10 (420/hpf vs 1041/hpf; p-value <0.001).

Conclusion: Apratoxin S10 leads to decreased tumor proliferation and tumor size in PDX models of PDAC. The drug concentrates in exocrine organs allowing it to reach therapeutic levels in pancreatic tumors. Apratoxin S10 can be an adjunct therapy to current cytotoxic therapies in pancreatic cancer.