1. SMAD4 LOSS IS ASSOCIATED WITH RESPONSE TO NEOADJUVANT CHEMOTHERAPY WITH THE AUTOPHAGY INHIBITOR HYDROXYCHLOROQUINE IN PATIENTS WITH PANCREATIC ADENOCARCINOMA

Presenter: Pavan Rao MD | West Virginia University School of Medicine
P Rao, S Wen, N Fei, R Ramanathan, ME Hogg, A Zureikat, MT Lotze, N Bahary, AD Singhi, HJ Zeh, BA Boone

**Background:** SMAD4, a tumor suppressor gene, is inactivated or deleted in 60-90% of pancreatic adenocarcinomas (PDA). Loss of SMAD4 allows tumor progression by limiting cell cycle arrest and apoptosis and increasing metastases. SMAD4 deficient PDA cells are resistant to radiotherapy by upregulation of autophagy, a cell survival mechanism that allows intracellular recycling of macromolecules and organelles. Hydroxychloroquine (HCQ) is a known autophagy inhibitor, suggesting that HCQ treatment in SMAD4 deficient PDA may prevent therapeutic resistance induced by autophagy upregulation.

**Methods:** We retrospectively analyzed the SMAD4 status of PDA patients enrolled in two prospective clinical trials evaluating preoperative HCQ. The first dose escalation trial demonstrated the safety of preoperative gemcitabine with HCQ (NCT01128296). More recently, a randomized trial of gemcitabine/nab-paclitaxel +/- HCQ evaluated Evans Grade histopathologic response (NCT01978184). Immunohistochemistry of resected specimens for SMAD4 was previously performed. Patients not treated at the max HCQ dose (n=5), not resected (n=2) or with SMAD4 staining unavailable were excluded (n=10). The effect of SMAD4 loss on response to HCQ and chemotherapy was studied for association with clinical outcome. Fisher’s exact test and log-rank test were used to assess response and survival.

**Results:** 52 patients receiving HCQ with neoadjuvant chemotherapy and 24 patients receiving neoadjuvant chemotherapy alone were studied. Of the HCQ group, 25 patients had SMAD4 loss (48%), compared with 15 control patients (63%, p=0.32). 76% of HCQ treated patients with SMAD4 loss obtained a histopathologic response ≥2A, compared to only 37% with SMAD4 intact (p=0.006). In the control group, loss of SMAD4 was associated with a nonsignificant detriment in 3 year OS (25% vs. 78%, p=0.3) that was less apparent in patients treated with HCQ (46% vs. 47%, p=0.18).
Conclusion: The addition of HCQ to neoadjuvant chemotherapy in PDA may improve treatment response in patients with SMAD4 loss. Further study of the relationship between SMAD4, autophagy and treatment outcomes in PDA is warranted.
Scientific Session 1

2. ENHANCEMENT OF THE TUMOR MICROENVIRONMENT IMMUNE RESPONSE IN PANCREATIC DUCTAL ADENOCARCINOMA PATIENTS AFTER NEOADJUVANT THERAPY
Presenter: Theodoros Michelakos MD | Massachusetts General Hospital
T Michelakos, F Kontos, Y Sekigami, L Cai, V Villani, F Sabbatino, A Neyaz, C Fernández-del Castillo, MS Taylor, V Deshpande, DT Ting, M Qadan, JN Allen, JW Clark, TS Hong, DP Ryan, JY Wo, AL Warshaw, KD Lillemoe, S Ferrone, CR Ferrone

Background: Neoadjuvant FOLFIRINOX and chemoradiation have been utilized to downstage borderline and locally advanced pancreatic ductal adenocarcinoma (PDAC). In vitro studies and experiments in animal models have demonstrated that chemotherapy triggers a tumor antigen-specific immune response. Therefore, we evaluated whether neoadjuvant therapy induces an immune response towards PDAC.

Methods: Clinicopathologic variables were collected for surgically resected PDACs at an academic hospital (1998-2014). Neoadjuvant regimens included FOLFIRINOX with or without chemoradiation, 25Gy of proton chemoradiation, 50.4Gy of photon chemoradiation or no neoadjuvant therapy. Immunohistochemical analysis for HLA class I and class II expression and immune cell density (CD4+, FoxP3+, CD8+, Granzyme B+ cells and M2 macrophages) were correlated with clinicopathologic variables. The anti-tumor immune response in patients who received neoadjuvant 25Gy of protons, 50.4Gy of photons, and/or FOLFIRINOX followed by radiation therapy was compared to resected patients who were neoadjuvant therapy naïve.

Results: Two hundred forty-eight PDAC patients were evaluated with a median age of 64y; 50% were female. The frequency of HLA-A defects was significantly lower in the FOLFIRINOX cohort (p<0.001). HLA class II expression level was lowest in photon and highest in proton treated patients (p=0.004). The FOLFIRINOX cohort exhibited the most robust CD8+ T cell infiltration (p<0.001). FOLFIRINOX and proton patients had the highest CD4+ and lowest T regulatory (Treg) cell density, respectively. M2 macrophage density was significantly higher in the treatment-naïve group (p<0.001), in which dense M2 macrophage infiltration was an independent predictor of poor OS.

Conclusion: Neoadjuvant FOLFIRINOX induced the most significant immunologically relevant changes in the tumor microenvironment. It increased the CD8+ T cell density and reduced the frequency of HLA-A defects as well as the Treg cell and M2 macrophage density. Therefore, neoadjuvant FOLFIRINOX therapy may benefit from
combinations with checkpoint inhibitors, which can enhance patients' immune response.
Scientific Session 1

3. TARGETING GUT MICROBIAL DYSBIOSIS TO COUNTERACT TUMOR PERMISSIVE EFFECTS OF SMOKING ON PANCREATIC CANCER

Presenter: Prateek Sharma MBBS | University of Miami
P Sharma, T Jain, V Sethi, S Kurтом, P Roy, J Tao, H Jacob, A Ferrantella, B Giri, M Tarique, S Iyer, D Edwards, B Gomez, S Lavania, S Ramakrishnan, R Dawra, A Saluja, V Dudeja

**Background:** Smoking is a major risk factor for many cancers. Cigarette smoke contains numerous carcinogenic compounds but the molecular mechanisms involved in cancer progression due to smoking are still being actively investigated. Smoking results in alteration of gut-microbiome and our recent studies have demonstrated the role of gut-microbiome in progression of cancer. In this study, we aim to delineate the role of smoking induced dysbiosis in cancer promotion.

**Methods:** 6-8 week old C57BL/6 mice were randomized to receive antibiotics (to sterilize the gut) or saline with or without concurrent cigarette smoke exposure (CSE). CSE was given through smoking chamber to achieve total suspended particulate concentration of 200-250 mg/m3. After pre-exposure of 4 weeks, mice were injected subcutaneously with a cancer cell line; KPC (pancreatic cancer cell line); MC38 (colon cancer cell line) or MB49 (bladder cancer cell line). The tumors were measured serially with ongoing CSE. In another experiment, fecal microbiota transplantation (FMT) from control or smoke-exposed mice to WT mice (biweekly for 4 weeks) was done and KPC cancer cells were then given subcutaneously to further evaluate the role of gut microbiome in smoking induced PDAC progression. These experiments were repeated in Rag1-/- mice (mice which lack adaptive immune response) to understand the role of adaptive immune response in smoking induced promotion of tumor growth. In another experiment, smoking analogue Nicotine-derived nitrosamine ketone (NNK) was used to simulate smoke exposure. Two-month old genetically engineered KC mice (LSL-KrasG12D/+; Pdx-1-Cre) were randomized into four treatment arms (controls, NNK alone, antibiotics alone and NNK + antibiotics). Treatment was given for 2 months and animals were euthanized at 4 months age.

**Results:** Cigarette smoke exposure (CSE) significantly promoted tumor growth in all cancer cell lines. Depletion of gut-microbiome by antibiotics prevented smoke induced cancer progression, suggesting a smoking - gut microbiome - pancreatic cancer progression axis. Mice receiving FMT from smoke-exposed mice had higher mean tumor
burden than mice receiving FMT from control mice. When compared to WT mice, CSE neither increased tumor growth nor did gut-microbiome depletion decreased tumor growth in Rag 1/- mice, suggesting that smoking induced gut-microbiome alteration promotes tumor growth in an adaptive immune response dependent fashion. NNK-exposed KC mice had increased tumor progression compared to the other treatment arms and this effect was negated upon gut microbiome depletion. Stool analysis showed significant enrichment of the Bacteriodetes phyla as well as the genera Clostridium and Parabacteriodes in the NNK alone group.

**Conclusion:** Our study for the very first time ever provides insights into how smoking/smoking analogs and gut-microbiome interact to influence pancreatic cancer progression. Smoke exposure facilitates tumor progression but disappearance of the tumor permissive effects in concomitant antibiotic-treated mice highlights the significant role played by the gut-microbiome in mediating these effects. Targeting this dysbiosis through selective antibiotics or probiotics could be harnessed as a potential strategy to neutralize the detrimental effects of smoking on cancer.
Scientific Session 1

4. EVALUATING THE IMMUNE MODULATORY EFFECTS OF A TARGETED ANICANCER THERAPY, ACXT-3102, IN MURINE MODEL OF PANCREATIC CANCER
Presenter: Usman Y Panni MD  |  Washington University in St. Louis
UY Panni, J Herndon, D Spitzer, D DeNardo, WG Hawkins

Background: Pancreatic cancer (PC) is expected to become 2nd deadliest malignancy in the United States by 2030, and there is a desperate need for novel therapeutic strategies in order to improve PC outcomes. Modern approaches, including immunotherapy, have shown minimal efficacy in human PC. Recent studies have demonstrated that conventional and targeted anticancer drugs exhibit immunomodulatory effects on the tumor microenvironment in addition to their direct cytotoxic effects. This promising strategy can improve the efficacy of novel agents by combining them with select immunotherapeutic drugs and vice versa. ACXT-3102 is a small molecule therapeutic agent which has shown to provide efficient tumor control and prolonged survival with minimal off-site toxicities in murine PC models. ACXT-3102 binds to cancer cell-specific sigma2-receptors and blocks intracellular uptake of cysteine at cystine-glutamate transporter, leading to an increase in intracellular accumulation of reactive oxygen species, and causing ferroptosis. Here we assess the immunomodulatory effects of ACXT-3102 on tumor immune infiltrates in murine PC model.

Methods: A spontaneously derived orthotopic murine PC model (KP2.0) was established in age-matched C57BL/6 mice. Mice were treated with an every other day dosing regimen of ACXT-3102 for 10 days. At the end of the treatment, tumors were harvested and were analyzed using flow-cytometry.

Results: We observed a significant reduction in tumor volume and gross tumor weight in the mice treated with ACXT-3102. Simultaneously there was an increase in CD8+ T cell numbers, activation, and proliferation by flow-cytometry. We also noted a significant increase in CD4+ T cell population with a decrease in regulatory T cell population.

Conclusion: Our results uncover the significant impact ACXT-3102 has on the T cell infiltration and activation in the tumor microenvironment, in addition to controlling tumor growth. We believe that exploring these findings further in combination with immunotherapy may be a useful strategy in the treatment of human PC.
Figure 1: (A) Tumor volume and tumor weights in murine orthotopic model of PC, KP2, treated with vehicle and ACXT-3102. N=10/group. 
(B)(C)(D)(E) Flow cytometry analysis of CD8+ T cells, Ki67+ CD8+ T cells, Total CD4+ T cells and FOXP3+ CD4+ T cells in the TME. N=5/group, *p<0.05.
Scientific Session 1

5. HIGH-FAT, HIGH-CALORIE DIET PROMOTES PANCREATIC NEOPLASIA IN KRASG12D +/- MOUSE MODEL
Presenter: Zipeng Lu MD, PhD | The First Affiliated Hospital with Nanjing Medical University
Z Lu, G Wang, H Gao, L Yin, Y Gao, J Zhang, K Zhang, K Jiang, Y Miao

**Background:** Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related death worldwide, with an overall 5-year survival rate of less than 9%. Numerous studies suggested that type 2 diabetes (T2DM) is a risk factor for pancreatic cancer, but the mechanism remains to be elucidated.

**Methods:** T2DM was induced by a high-fat, high-calorie diet (HFCD) in our study. LSL-KRASG12D +/-; Pdx1-Cre (KC) mice was established to investigate the effects of T2DM on the development of pancreatic cancer.

**Results:** Our results suggested that after 35 weeks of feeding, the weight of the HFCD group was significantly higher than that of the normal diet (ND) group. Blood glucose, triglyceride, insulin and cholesterol levels in the HFCD group were significantly higher than those in the ND group. Immunohistochemical results showed that the proportion of normal pancreatic duct decreased significantly in the HFCD group. However, the proportion of intraepithelial neoplasia, as well as acinar ductal metaplasia was significantly increased, accompanied by increased cytokeratin 19 (CK19) staining area. In addition, the positive area of Masson’s staining in the pancreatic tissue of the HFCD group, representing interstitial collagen fibers, was also significantly increased.

**Conclusion:** Our results suggested that a HFCD contributed to obesity and metabolic disorders in mice similar to humans. This process accelerated the development of pancreatic cancer in mouse models with KRAS mutations. Our results provided a solid basis for further revealing the mechanisms of T2DM promoting the occurrence of pancreatic cancer and evaluating dietary and drug prevention strategies for the development of T2DM-related pancreatic cancer.
Scientific Session 1

7. ALIGNMENT OF STROMA FIBERS AND MICROVESSEL DENSITY DETERMINE OVERALL SURVIVAL IN PANCREATIC CANCER - AN ANALYSIS OF STROMA MORPHOLOGY

Presenter: Louisa R Bolm MD | University Medical Center Schleswig-Holstein, Campus Luebeck
L Bolm, P Zgurskiy, H Lapshyn, E Petrova, YK Vashist, S Deichmann, KC Honselmann, P Bronsert, T Keck, UF Wellner

Background: Desmoplasia is a main feature of pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to define simple histo-morphological stroma characteristics by dissecting different stroma components, and to evaluate their impact on local and systemic tumor spread and overall survival.

Methods: Patients undergoing oncologic resections with curative intent for PDAC were identified from a prospectively maintained database. Patient baseline parameters, histopathological factors and long-term overall survival were analyzed for the study. Histological specimens were re-evaluated for morphological stroma features as alignment of stromal fibers, fibroblast density, fibroblast morphology, stroma matrix density and microvessel density.

Results: A total of 108 patients were identified undergoing curative resection for PDAC in the period from 2011-2016. Median age was 67 years and 62% of the patients were male. Regarding stroma features, a total of 33 (30.6%) patients showed parallel alignment of stroma fibers while 75 (69.4%) had randomly oriented stroma fibers. As compared to parallel alignment, random orientation of stroma fibers was associated with larger tumor size (median 3.62 cm vs. median 2.87 cm, p=0.037), nodal positive disease (76.0% vs. 54.5%, p=0.040), higher margin positive resection rates (41.9% vs. 15.2%, p=0.008) and a trend for higher rates of T3/4 tumors (33.3% vs. 15.2%, p=0.064). In univariate analysis, patients with parallel alignment of stroma fibers had improved overall survival rates as compared to patients with random orientation of stroma fibers (42 months vs. 22 months, p=0.046). The combination of random orientation of stroma fibers and low vascular density was associated with impaired overall survival rates (16 months vs. 36 months, p=0.019). Tumor size (HR 1.348, 95%CI 1.159-2.114, p=0.036), N status (HR 1.568, 95%CI 1.260-2.621, p=0.022) and R status (HR 1.443, 95%CI 1.136-2.167, p=0.022) were further prognostic parameters in univariate survival analysis. Random orientation of stroma fibers and low microvessel density (HR 1.592, 95%CI 1.098-2.733, p=0.029) qualified as only independent prognostic factor.
Conclusion: Alignment of stroma fibers and vascular density are simple histomorphological feature serving as surrogate markers of local tumor progression dissemination and surgical resectability and determine prognosis in PDAC patients.
Scientific Session 1

8. UTILIZING OXALIPLATIN AND OLAPARIB TO DEVELOP AN IMMUNOGENIC MURINE PANCREATIC CANCER MODEL
Presenter: Usman Y Panni MD | Washington University in St. Louis
UY Panni, DR Cullinan, P Goedegebuure, KH Lim, DG DeNardo, WE Gillanders, WG Hawkins

Background: Immune checkpoint inhibitors have been successful in treating cancers such as melanoma, smoking-associated non-small cell lung cancer, and the efficacy of these agents is strongly correlated with the high mutational burden of these cancers. Some of these mutations lead to the expression of tumor-specific proteins known as neoantigens, which are recognized by T cells and are essential in generating a T cell-mediated antitumor immune response. In contrast, checkpoint immunotherapy has not been effective in pancreatic cancer (PC), which is characterized by a low mutational burden, fewer neoantigens, and decreased T cell infiltration into the tumor microenvironment. Evaluation of strategies that can increase the mutational burden of PC, and render it sensitive to the effects of checkpoint immunotherapy is currently being explored by multiple groups. Here we utilize a novel strategy of treating a murine PC cell line, KP2.0, which is a Kras and P53 driven cell line with a low mutational burden and has poor responsiveness to checkpoint immunotherapy. We treated KP2.0 with oxaliplatin and a PARP inhibitor in vitro to increase the intrinsic mutational burden of the tumor cells. We hypothesize that treating the KP2.0 cell line with this strategy will increase the overall mutational burden and expressed neoantigens, making it sensitive to the effects of checkpoint immunotherapy.

Methods: We treated KP2.0 cells in vitro with nonlethal concentrations of oxaliplatin and olaparib (OXPARPi) for four months. We then utilized single-cell cloning to generate six subsequent daughter cell lines (A-F) from the treated KP2-OXPARPi cell line. Each of these six cell lines had different tumor mutational burden and number of predicted neoantigens, as confirmed by whole-exome sequencing and in silico prediction tools. The in vivo growth kinetics of each of the cell lines was determined in a subcutaneous murine PC model. RT-PCR analysis was performed on harvested tumors to confirm the retention of neoantigens.

Results: Each of the KP2- OXPARPi cell lines exhibited different tumor growth and progression rates in mice, with cell line A identified as most aggressive, and cell line C as least aggressive. RT-PCR analysis performed on harvested tumor tissue showed retention
of certain neoantigens in the tumors. To determine if the increase in mutational burden can lead to improved efficacy of immune checkpoint inhibitors, we established a subcutaneous tumor model using KP2-OXPARPi cell line A. The tumor-bearing mice were treated with anti-PD1 and anti-CTLA4 till Day 32 of implantation. The treated tumors showed a significant reduction in tumor growth. The tumor volumes and tumor weights were also significantly reduced in the treatment group.

**Conclusion**: Our results uncover a novel strategy to render an otherwise nonimmunogenic murine PC cell line immunogenic by treating it with clinically relevant chemotherapy agents. We believe that exploring these findings further by utilizing vaccination strategies in combination with immunotherapy will help us better understand the role tumor mutational burden can have in the treatment of human PC.

![Graphs showing tumor growth and weight changes](image-url)

**Figure 1**: (A) Tumor growth curve (XY graph) in subcutaneous tumor model. (B),(C) Tumor volume and tumor weights (Bar graph) measured following treatment with vehicle and anti-PD1 + anti-CTLA4 on Day 33. N=10/group. *p<0.05
9. CHARACTERIZATION OF MACROPHAGE ISOCITRATE DEHYDROGENASE 1
Presenter: Jonathan J Hue MD | Case Western Reserve University School of Medicine
J Hue, A Vaziri-Gohar, S Chelstowska, H Graor, S Huang, J Winter

Background: Pancreatic cancer remains one of the most lethal cancers and few novel effective treatments have come to fruition in recent years. Immune cells, including macrophages, are important in tumor growth and metastasis. Tumor-associated macrophages (TAMs or M2) rely on oxidative phosphorylation for energy production, whereas pro-inflammatory macrophages (M1) rely mainly on glycolysis. Pancreatic cancer has been shown to have a nutrient deplete tumor microenvironment (TME) which requires cells to detoxify reactive oxygen species. Our unpublished work has shown that isocitrate dehydrogenase 1 (IDH1), a cytosolic enzyme that produces NADPH, is important for this process in a pancreatic cancer model. However, it still remains unclear whether IDH1 also plays a role in regulating cellular metabolism and immunosuppressive properties of TAMs for pancreatic cancer pathogenesis.

Methods: Bone marrow-derived macrophages were generated from immunocompetent C57BL/6 mice, ages 6-10 weeks. Naïve macrophages (M0) were stimulated in vitro with either interferon-gamma plus lipopolysaccharide (M1 polarization) or interleukin-4 (M2 polarization). Cells were grown in complete media or low nutrient conditions (2.5 mM glucose or 0.5 mM glutamine), which mimic the TME. IDH1 expression was determined using quantitative RT-PCR and mRNA fold changes (FC) were normalized to M0 expression in complete media. Cell activation phenotypes were assessed using a combination of multi-color flow cytometry and qRT-PCR analysis. Cell viability was determined using PicoGreen Assay and 7-AAD staining by flow cytometry analysis.

Results: Compared to IDH1 expression in naïve macrophages (FC=1.0), M2 stimulated macrophages exhibited significantly elevated IDH1 expression (FC=5.44, p<0.001), whereas expression in M1 stimulated macrophages was significantly reduced (FC=0.28, p<0.001). Intriguingly, naïve macrophages grown in either low glucose (2.5 mM) or low glutamine (0.5 mM) conditions appear to increase the expression of IDH1 (FC=3.09, p<0.001; FC=3.67, p<0.001, respectively) and have increased levels of a typical M2 marker, CD206 (FC=2.17, p=0.003; FC=2.42, p=0.006, respectively). These findings occurred to a lesser extent in the pro-inflammatory M1 phenotype under the same growth conditions.
**Conclusion:** Under nutrient deprivation, macrophages tend to have an enhanced protumoral M2 phenotype, suggesting that the nutrient deprived pancreatic TME may lead to increased proportions of tumor-associated M2 macrophages. Importantly, our preliminary data also show that the expression of IDH1 was increased in M2 macrophages. Collectively, the intervention of protumoral M2 macrophages by targeting IDH1 could be a potential therapeutic strategy to alter the immunosuppressive microenvironment, suppress tumor growth, and decrease metastatic potential in pancreatic cancer.
10. GEOGRAPHIC VARIATION IN ATTITUDES REGARDING LOCALLY ADVANCED PANCREATIC CANCER MANAGEMENT

Presenter: Bradley N Reames MD, MS | University of Nebraska Medical Center
BN Reames, AB Blair, RW Krell, A Ejaz, VP Groot, G Gemenetzis, JC Padussis, SP Thayer, M Falconi, CL Wolfgang, MJ Weiss, C Are, J He

Background: Evidence to guide management of locally advanced pancreas cancer (LAPC) is limited to retrospective reports. Numerous studies suggest attitudes regarding LAPC management are inconsistent between surgeons and across institutions. We sought to examine the influence of geographic practice location on surgeon attitudes regarding management of LAPC.

Methods: An extensive electronic survey was distributed by email to an international cohort of pancreas surgeons. Data collected included practice characteristics, preferences for staging and management, and 6 clinical vignettes (with detailed videos of post-neoadjuvant arterial and venous CT imaging) to assess attitudes regarding eligibility for surgical exploration. Descriptive and comparative statistics were used to examine differences in attitudes across geographic locations of practice.

Results: A total of 153 eligible responses (estimated response rate: 10.6%) were received from 4 continents: North and South America (NSA, combined N=94, 61.4%), Europe (EUR, N=25, 16.3%), and Asia (N=34, 22.2%). Median duration of practice was 12 years (IQR 6-20) and most participants are considered high volume surgeons (>10 pancreatectomies/year, 86.3%) working at high volume hospitals (>25/year, 88.9%). Examination of attitudes regarding LAPC management revealed numerous significant differences across practice locations. Participants from Asia more frequently prefer MRI (67.6%) and PET/CT (44.1%) for initial staging, versus NSA (23.4% and 8.5%) and EUR (32% and 16%, P < 0.001 for both). Neoadjuvant chemotherapy is “always” recommended by a majority of participants in NSA (81.9%) and EUR (68.0%), but a minority of those in Asia (47.1%, P=0.001). The preferred duration of neoadjuvant systemic therapy varied: participants from Asia commonly prefer 2 months (61.8%), while NSA participants prefer 4 months (52.1%), and responses from EUR were mixed (P=0.006). Participants from EUR were less likely to recommend neoadjuvant radiation (32% never recommend), compared to those from NSA (3.2% never recommend) and Asia (17.6% never recommend, P < 0.001). Participants offering minimally-invasive surgery from NSA and EUR were more likely to use a robotic approach (48% and 75%, respectively) than those
from Asia (33.3%, P=0.01). Participants from Asia were less likely to consider isolated liver (67.6%) or lung (61.8%) metastases contraindications to exploration, versus those from NSA (90.4% and 88.3%) and EUR (72% and 72%, P < 0.005 for both), and this corresponded to a greater propensity to consider exploration in a vignette of oligometastatic disease (56.7%, vs. 25.6% for NSA and 43.5% for EUR, P=0.007). For all three groups, concern regarding arterial involvement was the most common reason to avoid exploration in 6 vignettes. Participants from Asia commonly preferred continuing current chemotherapy as an alternative recommendation for 6 vignettes, while those from NSA frequently recommended clinical trial options, and responses from EUR were mixed.

**Conclusion:** In an international survey of high volume pancreas surgeons, attitudes regarding LAPC management varied across geographic locations of practice. Better evidence is needed define the optimal management approach to LAPC.
Scientific Session 1

11. THE ROLE OF POSITRON EMISSIOAN TOMOGRAPHY SCAN DERIVED PARAMETERS IN PREDICTION OF RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY FOR BORDERLINE RESECTABLE AND LOCALLY ADVANCED PANCREATIC CANCER

Presenter: Woohyung Lee | Asan Medical Center
SC Kim, W Lee

Background: Although neoadjuvant chemotherapy (NACT) became the main stream of management for borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC), adequate evaluating markers for response after NACT was not confirmed yet.

Methods: BRPC and LAPC patients who underwent surgery with positive emission tomographic (PET) scan in both pre-NACT and post-NACT were included between 2012 and 2019. The risk factors poor tumor regression grade (TRG), and worse prognosis were evaluated including PET derived parameters.

Results: Of 189 patients, FOLFIRINOX and gemcitabine were administered in 143 and 46 patients, respectively. And 54 patients were selected for PET scan. Marked response of TRG was related with relative difference of SUVmax and SUVpeak (hazard ratio [HR]; 0.019, 95% confidence interval [CI]; 0 - 0.423, p = 0.028). Prognostic factors were found such as TLG (HR; 1.670, 95% CI; 1.102 – 2.531, p = 0.016), MTV (HR; 1.716, 95% CI; 1.102 – 2.673, p = 0.017) in post-NACT state and relative difference during NACT as well as neoadjuvant cycle (HR; 0.762, 95% CI; 0.605 – 0.961, p = 0.022), and NACT regimen (HR; 0.205, 95% CI; 0.050 – 0.840, p = 0.028) in univariate analysis.

Conclusion: The changing parameters of PET are helpful to evaluate response after NACT. However, confirmatory study will be needed for the small number of enrolled patients.
Scientific Session 1

12. POSTOPERATIVE CHEMOTHERAPY BENEFITS PATIENTS WHO RECEIVED PREOPERATIVE THERAPY AND PANCREATECTOMY FOR PANCREATIC ADENOCARCINOMA

Presenter: Giampaolo Perri MD | University of Texas MD Anderson Cancer Center
G Perri, L Prakash, W Qiao, GR Varadhachary, R Wolff, D Fogelman, M Overman, S Pant, M Javle, EJ Koay, J Herman, M Kim, N Ikoma, C Tzeng, JE Lee, MHG Katz

Background: Data to support administering postoperative chemotherapy to patients who received preoperative therapy are lacking. We sought to determine whether postoperative chemotherapy following preoperative therapy and pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) prolongs survival.

Methods: All patients with PDAC who underwent pancreatectomy following preoperative therapy between 2010 and July 2017 at The University of Texas MD Anderson Cancer Center were identified. To control for selection bias, patients who received postoperative therapy and patients who did not were matched by propensity scores based on factors associated with the use of postoperative chemotherapy.

Results: Among 245 patients treated with a median of 4 cycles of preoperative treatment and pancreatectomy, 155 (63%) initiated postoperative chemotherapy and 90 (37%) did not. Patients who received postoperative therapy had a higher median CA 19-9 level before surgery, larger median tumor diameter, higher rate of extrapancreatic invasion, and lower rate of pathologic major response. The propensity-matched cohort comprised 122 patients: 61 who received postoperative chemotherapy and 61 who did not. The median OS and RFS for patients who received postoperative therapy were 42 and 17 months, respectively, vs 32 and 12 months for patients who did not (OS: P= 0.06; RFS: P= 0.04). Postoperative therapy was marginally associated with a longer OS (HR 0.55, 95%CI 0.29-1.01; P= 0.05) and significantly associated with a longer RFS (HR 0.55, 95% CI 0.29-0.96; P= 0.04).

Conclusion: Despite being administered more frequently to patients with poor prognostic factors, postoperative chemotherapy following preoperative therapy and pancreatectomy for PDAC was of clinical benefit.
Overall Survival (%)

Postoperative therapy:
- No
- Yes

$P = 0.06$

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No 61 43 22</td>
<td>11 3 1 0</td>
</tr>
<tr>
<td>Yes 01 49 20</td>
<td>12 4 1 0</td>
</tr>
</tbody>
</table>
Scientific Session 1

13. AGGRESSIVE SURGERY FOR SELECTED PATIENTS WITH PANCREATIC CANCER AND ISOLATED LIVER METASTASIS
Presenter: Minako Nagai | Johns Hopkins University School of Medicine
WR Burns, M Nagai, D Ding, MJ Wright, ED Thompson, AA Javed, MJ Weiss, RH Hruban, J Yu, RA Burkhart, J He, JL Cameron, CL Wolfgang

Background: Patients with pancreatic ductal adenocarcinoma (PDAC) and liver metastasis are currently treated with palliative chemotherapy, whereas similar patients with metastatic colorectal cancer are considered for aggressive surgery. Recent advances in systemic control have provided improved outcomes in Stage IV PDAC with selected patients mirroring outcomes in metastatic colorectal cancer. We explored the role of aggressive surgery for metastatic pancreatic cancer in the era of multi-agent chemotherapy.

Methods: Using a prospective database, we identified PDAC patients undergoing liver resection for isolated metastasis. The primary outcome was overall survival (OS) and we assessed treatment factors and clinicopathological variables associated with survival.

Results: From 2000-2019, we identified 47 patients who underwent curative-intent surgery for pathologically-confirmed metastatic PDAC to the liver. Median followup was 18.1 months from diagnosis and 9.5 months following the completion of surgery. The 1- and 2-year survival rates from diagnosis were 78% and 47%, respectively, with a median OS of 21.9 months from diagnosis and 12.3 months from surgery. The majority of patients (n=37; 79%) had simultaneous pancreas and liver surgery, whereas nine patients underwent liver resection during an aborted exploratory surgery followed by systemic chemotherapy and interval pancreatectomy; one patient underwent liver metastasectomy after pancreatic surgery. The timing of liver metastasectomy was not associated with survival. Thirty-two patients (68%) received preoperative chemotherapy. The majority (n=27; 84%) were treated with multi-agent chemotherapy including FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) or gemcitabine plus nab-paclitaxel. Of the 32 patients who were treated with preoperative chemotherapy, median OS was 30.7 months from diagnosis. Median duration of preoperative chemotherapy was 7.5 months. Thirty-three patients underwent planned liver and pancreatic surgery with median OS was 26.3 months from diagnosis and 17.4 months from surgery, whereas 14 patients underwent unplanned resection of radiographically-occult liver metastasis during pancreatectomy with
median OS of only 8.7 months. Of the 33 patients who underwent planned surgery, there were 4 patients who underwent upfront surgery due to an uncertain preoperative diagnosis. The remaining cohort of 29 patients, who underwent planned resection after preoperative chemotherapy, was best suited for aggressive surgery with a median OS was 38.1 months from diagnosis and 24.1 months from surgery. Several factors were associated with prolonged survival on univariate analysis, but only the use of preoperative chemotherapy (HR=7.1; P < 0.01) and moderate-/well-differentiation of the primary tumor (HR=3.7; P < 0.01) were associated with prolonged survival from diagnosis in both univariate and multivariate analysis. Lymph node metastases, lymphovascular invasion, perineural invasion, response to preoperative therapy, number of liver metastasis, and extent of liver surgery were not associated with survival. There was complete followup for 38 patients, of which 30 patients (79%) developed recurrent PDAC. Most common recurrence site was liver (n=21) followed by local recurrence (n=12); fourteen patients had multiple sites. Median relapse-free survival was 6.1 months.

**Conclusion:** In selected patients with pancreatic cancer and isolated liver metastasis, surgical resection of the pancreatic and liver tumors can result in meaningful survival. Prospective trials to evaluate the role of aggressive surgery in such patients are warranted.
14. PANCREATIC CANCER RISK DETERMINATION IN PATIENTS WITH NEW-ONSET TYPE 2 DIABETES MELLITUS

Presenter: Ki J Lee | Lahey Hospital and Medical Center
KJ Lee, LL Price, L Scheuer, S Curry, M Hodge, T Schnelldorfer

Background: New-onset type II diabetes mellitus is a well-established early sign of pancreatic cancer. Currently there is a knowledge gap in the characterization of pancreatic cancer-associated new-onset type II diabetes mellitus in comparison to new-onset type II diabetes mellitus from other etiologies.

Methods: In this retrospective case-control study, all patients with new-onset type II diabetes mellitus treated at a single institution with a follow-up of at least 2 years between 2003 and 2013 were included. Patients were divided into 2 groups depending on whether they were diagnosed with pancreatic cancer within 2 years after diagnosis of diabetes (cases) or had no evidence of pancreatic cancer throughout their follow-up (controls). A 2:1 matching occurred due to an overproportioned number of controls, creating a study cohort of 326 controls and 163 cases. Conditional logistic regression univariate analyses and multivariable logistic regression modeling were used for group comparison of clinical features.

Results: The control group had a mean age of 63.0 (SD=13.6) and 41.1% were male. The case group had a mean age of 67.9 (SD=10.3) and 41.7% were male.
Eight clinical variables with reached significance with a p-value of less than 0.1 on conditional logistic regression univariate analysis and were included in the multivariable model. The included clinical variables had at least 140 pairs of data. The results from the multivariable model with backward selection (Table 1 with odds ratio and 95% confidence interval) identified older age, chronic pancreatitis, arterial vascular disease, smoking, and family history of pancreatic cancer as independent risk factors for future development of pancreatic cancer in the setting of new-onset type II diabetes mellitus. However, family history of type II diabetes mellitus and alcohol use seemed to reduce the risk of harboring pancreatic cancer.

Conclusion: Within the large group of patients with new-onset type II diabetes mellitus, special attention should be given to patients with the following characteristics: age greater than 70, chronic pancreatitis, arterial vascular disease, smoking, and family history of pancreatic cancer. These patients are at increased risk of harboring
pancreatic cancer as the underlying cause for the new-onset type II diabetes mellitus. In this patient cohort, especially when more than one risk factor is present, consideration should be given to undergo pancreatic cancer screening.

Table 1. Multivariable Model with Backward Selection Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>&lt;60</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>1.29 (0.50, 3.32)</td>
<td>0.60</td>
</tr>
<tr>
<td>70-79</td>
<td>7.53 (2.19, 25.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥80</td>
<td>3.98 (1.00, 15.75)</td>
<td>0.05</td>
</tr>
<tr>
<td>family_history_diabe</td>
<td>0.17 (0.07, 0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>chronic_pancreatitis</td>
<td>31.24 (2.55, 382.79)</td>
<td>0.007</td>
</tr>
<tr>
<td>arterial_vascular_di</td>
<td>8.99 (3.51, 23.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>alcohol</td>
<td>0.37 (0.16, 0.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>smoker</td>
<td>3.70 (1.10, 12.44)</td>
<td>0.03</td>
</tr>
<tr>
<td>nunrelpac (0 vs &gt;0)</td>
<td>16.61 (1.55, 177.59)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Scientific Session 1

15. THE INFLUENCE OF EDUCATION AND SUPPORT CLASS ROOM FOR PANCREATIC CANCER PATIENTS AND FAMILY BY THE MEDICAL TEAM “SUIGAN-KYOUSHTSU“: A QUESTIONNAIRE SURVEY

Presenter: Masashi Kishiwada MD, PhD | Mie University School of Medicine
M Kishiwada, A Hayasaki, K Gyoten, T Fujii, Y Iizawa, A Tanemura, Y Murata, N Kuriyama, H Sakurai, S Mizuno

Background: Education and support classroom for pancreatic cancer patients and family by the medical team “Suigan-Kyoushitsu” was started from December 2012 in our institution. The member consists of six occupations: Doctor (Dr), pharmacist (Ph), dietitian (D), nurse (Ns), medical social worker (MSW) and clinical psychologist (CP). It is composed of a lecture and a conversation for 60 minutes in each occupation’s classroom. We evaluated the influence of Suigan-Kyoushitsu by questionnaire survey.

Methods: We held 120 classrooms and obtained the results of a questionnaire survey from 349 participants since December 2013 to December 2018. Questionnaire survey included five questions: Q1; were you able to deepen information and knowledge? Q2; did you become able to face up to pancreatic cancer treatment? Q3; did you find that there were many medical team staff for pancreatic cancer treatment? Q4; did you want to continue participating in Suigan-Kyoushitsu? Q5; did you have good conversation among participants? We compared feeling for pancreatic cancer treatment before and after participation in Suigan-Kyoushitsu by using face scale (five grading system).

Results: From Q1 to Q4, more than 80% affirmative opinions were obtained from classrooms of all occupations. There was different result in Q5. Yes; Dr. 83%, Ph. 73%, D 75%, Ns. 95%, MSW 70%, and CP 88%. The nurses and clinical psychologists' committees received high evaluation. It was considered that nurses had introduced the salon style with the participation of multiple staff members, and that clinical psychologists had introduced relaxation techniques. The changes of feeling in total lecture after the participation significantly improved from 3.0±0.7 points with 3.9±0.5 points (p<0.01).

Conclusion: Suigan-Kyoushitsu in the medical team obtained good evaluation from questionnaire survey and it seem to be useful for pancreatic cancer patients and family. It is necessary to devise a method of holding Suigan-Kyoushitsu each occupation.
16. IMPROVED OUTPATIENT COMMUNICATION DRAMATICALLY DECREASES UNPLANNED READMISSION IN NECROTIZING PANCREATITIS

Presenter: Thomas K Maatman MD | Indiana University School of Medicine

Background: Unplanned readmission rates in necrotizing pancreatitis (NP) are extremely high (72%) with a reported incidence among the highest of any medical disease. Recent work has identified several potentially preventable specific causes of unplanned readmission in NP. We hypothesized that intensive outpatient communication would identify developing problems and decrease unplanned hospital readmission.

Methods: Retrospective analysis of all NP patients treated at a single institution between 2016 and 2019 compared patients two years before (NP-Pre, 2016-2018) and one year after (NP-Post, 2018-2019) the establishment of a dedicated pancreatitis nurse coordinator (PanRN). Frequency and specific type of outpatient communication with the PanRN was recorded and defined as either PanRN-driven or patient-driven communication. The incidence, frequency, and causes of unplanned hospital readmission and emergency room (ER) visits were compared. P-values < 0.05 were accepted as statistically significant.

Results: A total of 178 NP patients were treated during the study period. The two-year NP-Pre group consisted of 112 patients and the one-year NP-Post group consisted of 66 patients. No differences between groups were observed in age, sex, comorbidities, pancreatitis etiology, organ failure, infected necrosis, index admission length of stay, disease duration, or mortality. A mean of 5.4 (SEM, 0.2) outpatient communications/patient with the PanRN were observed in the NP-Post group. Communication was PanRN-driven 87% of the time and patient-driven 13% of the time. The overall incidence of unplanned readmission decreased significantly from 64% (NP-Pre) to 45% (NP-Post), P = 0.02. The incidence of ER visits was similar in the two time periods (NP-Pre, 22%; NP-Post, 20%; P = 0.7). A comparison of the most common indications for unplanned hospital readmission between groups is shown in Figure 1. Early identification and outpatient management of feeding tube malfunction (18 events), percutaneous drain malfunction (6 events), and failure to thrive (1 event) prevented 25 ER visits or unplanned hospital readmissions in the NP-Post group.
**Conclusion**: Improved outpatient communication identifies treatable problems and significantly decreases unplanned readmission in necrotizing pancreatitis patients.