1. PREOPERATIVE SINGLE-DOSE METHYLprednisolone versus Placebo for Elective Major Liver Resection in Adults: A Randomized Controlled Trial
CG Ball, AK Bressan, S Isherwood, OF Bathe, E Dixon, FR Sutherland
Presenter: Chad Ball MD, MSc | University of Calgary

Background: Hepatic resections are associated with a significant acute systemic inflammatory response. This effect subsequently correlates with postoperative morbidity, mortality and length of recovery. Multiple small trials have proposed that the administration of glucocorticoids may modulate this effect. The primary aim of this study was to evaluate the efficacy of a single preoperative dose of methylprednisolone for preventing postoperative complications after major liver resections.

Methods: This study was a parallel, dual-arm, double-blind randomized controlled trial. Adult patients undergoing elective major hepatic resection (>3 segments) at a quaternary care institution were included (2013-2019). Patients were randomly assigned to receive a single preoperative 500mg dose of methylprednisolone versus placebo. The main outcome measure was postoperative complications after liver resection, within 90 days of the index operation. Standard statistical methodology was employed (p<0.05 = significant).

Results: A total of 151 patients who underwent a major hepatic resection were randomized (mean age = 62.8 years; 57% male; body-mass-index = 27.9). No significant differences were identified between the intervention and control groups (age, sex, body-mass-index, preoperative comorbidities, hepatic function, ASA class, portal vein embolization rate) (p>0.05). Underlying hepatic diagnoses included colorectal liver metastases (69%), hepatocellular carcinoma (18%), non-colorectal liver metastases (7%), and intrahepatic cholangiocarcinoma (6%). There was a significant reduction in the overall incidence of postoperative complications in the methylprednisolone group (31.2% vs. 47.3%; p=0.042). Patients in the glucocorticoid group also displayed less frequent organ space surgical site infections (6.5% vs. 17.6%; p=0.036), as well as a shorter length of hospital stay (8.9 vs. 12.5 days; p=0.015). Postoperative serum bilirubin and prothrombin time-international normalized ratio (PT-INR) levels were also lower in the glucocorticoid group (p=0.03 and 0.04 respectively). Multivariate analysis did not identify any additional significant modifying factor relationships (estimated blood loss, duration of surgery, hepatic vascular occlusion (rate or duration), portal vein embolization, drain use, etc.) (p>0.05).

Conclusion: A single preoperative dose of methylprednisolone significantly reduces the length of hospital stay, postoperative serum bilirubin and PT-INR, as well as infectious and overall complications following major hepatectomy.
2. PERSISTENT CIRCULATING TUMOR CELLS AT ONE YEAR AFTER ONCOLOGIC RESECTION OF PANCREATIC CANCER PREDICT RECURRENCE

CL Wolfgang, D Ding, A Hasanain, FV Oosten, G Gemenetzis, V Groot, J Tenior, AA Javed, M Wright, J Yu, J Cameron, M Weiss, WR Burns, R Burkhart, L Zheng, J He

Presenter: Ding Ding MD, ScM | Johns Hopkins University School of Medicine

**Background:** Circulating tumor cell (CTC) subtypes have been used as new biomarkers to predict early or late recurrence and response to treatment for pancreatic cancer. A subset of patients have persistent presence of CTCs beyond 6 months of resection. Since the estimated halflife of CTC are estimated to be 15 minutes, persistent CTC is presumed to be an indicator of minimal residual disease. The fate of this cohort of patients is unknown. Herein, we want to determine whether the presence of CTC subtypes found in recurrence free patients approximately 12 months post-surgery was associated with recurrence.

**Methods:** The study included patients in our recently published prospective CLUSTER clinical trial who did not have clinical evidence of recurrence and had CTC testing results between 9 and 15 months after surgery. Both epithelial CTC (eCTC) and epithelial/mesenchymal CTC (mCTC) subtypes were used to predict recurrence from the CTC testing time within 9-15 months after surgery. Kaplan-Meier curve, log-rank test, and Cox model were used for survival analysis.

**Results:** Of the 129 patients enrolled in CLUSTER trial, a total of 28 patients were included in this final study. The recurrence rate per person-month of follow-up was 14.8% (7 recurrences per 48.11 months) for the high eCTCs (≥5) group while only 4.2% (9 recurrences per 213.71 months) for the low eCTC (<5) group. Low eCTCs was associated with longer recurrence free survival since date of CTC testing compared to high eCTCs (median = not reached vs. 3.78 months, p=0.007). Furthermore, low eCTCs was associated with longer overall survival since CTC testing date compared to high eCTC (median = not reached vs. 12.30, p=0.027). Negative mCTC (≥0) was also associated with longer recurrence free survival (median = not reached vs. 4.23, p=0.015) since date of CTC testing. On multi-variable cox model including pathological covariates, neo-adjuvant, and adjuvant chemotherapy status, high eCTCs was a risk factor for recurrence since date of CTC testing (Hazard Ratio = 4.41; 95% CI [1.13, 17.23]; p=0.033). Positive mCTCs was also associated with a 10.25-fold risk (Hazard ratio = 10.25; 95% CI [1.83, 15.34]; p=0.008) of recurrence since date of CTC testing compared to negative mCTCs.

**Conclusion:** Positive mCTCs and high eCTCs in recurrence free patients around 12 months after surgery were independent prognostic factors for earlier recurrence since date of CTC testing, which could be used a putative biomarker to guide prospective treatment.
3. PATIENT-SPECIFIC OPIOID VOLUME CALCULATIONS REDUCE DISCHARGE PRESCRIPTIONS AFTER HEPATO-PANCREATO-BILIARY SURGERY


Presenter: Ryan Day MD | The University of Texas MD Anderson Cancer Center

Background: Patients who undergo hepato-pancreato-biliary (HPB) surgery and receive discharge opioid prescriptions beyond their actual needs are at risk for persistent use and diversion to family and community. In the context of the United States opioid epidemic, this study’s aim was to quantify and compare HPB surgery discharge prescribing patterns balanced against 30-day refill rates to compare a novel standardized prescription calculation vs. usual care.

Methods: This is a non-randomized retrospective cohort study of consecutive HPB operations at a Comprehensive Cancer Center (September 2018 – June 2019). These dates were based on departmental opioid reduction education initiatives in August 2018, which included the introduction of a novel patient-specific “5x multiplier” concept, wherein patients received 5-times their actual opioid use in the last 24 hours of their inpatient stay. This concept was adopted by a voluntary proportion of our individual HPB providers. Thus, there were two prescribing patterns: a usual care group which typically received a round number of opioid pills based on provider preference vs. the “5x multiplier” calculation. Refills were abstracted from the electronic medical record. Actual opioid doses (oral morphine equivalents, OME) in the last 24 hours of inpatient stay and discharge prescriptions were recorded and converted with institution-approved conversion tables (e.g., one 50-mg tramadol equals 5mg OME, and one 5-mg oxycodone equals 7.5mg OME). Descriptive statistics were used to summarize and compare the usual care and 5x-multiplier cohorts.

Results: There were 278 consecutive HPB operations for 276 unique patients. These included 152 (55%) liver and 126 (45%) pancreas resections. Of 278 operations, 125 (45%) were in the 5x-multiplier cohort. Both groups had similar demographic and peri-operative characteristics including length of stay and use of non-opioid medication bundles. The median OME consumed during the last 24 hours before discharge was 10mg (range 0-360mg; IQR 4-20mg) in the total 278 index hospitalizations. The median last 24-hr OME was 10mg (range 0-200mg, interquartile range [IQR] 5-20mg) for usual care vs. 10mg (range 0-360mg, IQR 0-20mg) for the 5x-multiplier. The median discharge prescription OME was 3-times higher in the usual care group (150mg, range 0-3,150mg, IQR 100-150mg, p<0.001). Despite this reduction, rates of opioid refills within 30 days were similar for the usual care and 5x-multiplier groups (20.9% vs. 16.8%, p=0.385). Pancreas surgery patients were more likely to receive a postoperative 30-day refill compared to liver surgery patients (32/126, 25%, vs. 21/152, 14%, p<0.001). Among all patients, 69 (25%) patients used zero OME in the last 24 hours. However, 31/69 (45%), were still discharged with opioids. Using the 5x multiplier for the 153 usual care discharge prescriptions would have hypothetically saved 15,761mg OME, or 3,152 pills of 50-mg tramadol over this 10-month study period.

Conclusion: In patients undergoing HPB operations, a simple, reproducible strategy using a patient-specific 5x-multiplier of actual last 24-hour inpatient opioid consumption reduced median discharge opioid prescriptions by 67% over usual care, with no measurable increase in refills. The next step will be a department-wide prospective quality improvement project implementing this novel 5x multiplier.
Table 1. Comparison of patient characteristics managed in usual care and 5x pathways

<table>
<thead>
<tr>
<th></th>
<th>Usual Care (n=153)</th>
<th>5X Group (n=125)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.3 (48.4 – 68.6)</td>
<td>59.2 (49.6 – 68.5)</td>
<td>0.618^</td>
</tr>
<tr>
<td>BMI</td>
<td>25.8 (22.8 – 29.6)</td>
<td>26.5 (22.8 – 29.9)</td>
<td>0.643^</td>
</tr>
<tr>
<td>Female</td>
<td>74 (48.4%)</td>
<td>59 (47.2%)</td>
<td>0.846</td>
</tr>
<tr>
<td>Preoperative Opioids</td>
<td>29 (22.6%)</td>
<td>12 (18.4%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Liver operation</td>
<td>88 (57.5%)</td>
<td>64 (51.2%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Laparoscopic or robotic operation</td>
<td>24 (25.3%)</td>
<td>22 (20.7%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Combination operation</td>
<td>14 (9.2%)</td>
<td>19 (15.2%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Regional Nerve Block</td>
<td>72 (47.1%)</td>
<td>75 (60.0%)</td>
<td>0.032</td>
</tr>
<tr>
<td>Epidural</td>
<td>46 (30.1%)</td>
<td>27 (21.6%)</td>
<td>0.111</td>
</tr>
<tr>
<td>Major Complication</td>
<td>28 (18.3%)</td>
<td>15 (12.0%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Readmission</td>
<td>28 (18.3%)</td>
<td>18 (14.4%)</td>
<td>0.384</td>
</tr>
<tr>
<td>&gt;=2 Non-Opioid Meds Bundled with Opioids</td>
<td>122 (79.7%)</td>
<td>97 (77.6%)</td>
<td>0.664</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>4 (3 – 6)</td>
<td>5 (3-6)</td>
<td>0.518^</td>
</tr>
<tr>
<td>Refills within 30 days</td>
<td>32 (20.9%)</td>
<td>21 (16.8%)</td>
<td>0.385</td>
</tr>
<tr>
<td>Last 24 hours OME, mg</td>
<td>10 (5 – 20)</td>
<td>10 (0 – 20)</td>
<td>0.360^</td>
</tr>
<tr>
<td>Initial Discharge OME, mg</td>
<td>150 (100 – 150)</td>
<td>50 (0 – 100)</td>
<td>&lt;0.001^</td>
</tr>
</tbody>
</table>

^ = Mann-Whitney U test, * = Fisher’s Exact Test, All other chi square.

BMI = Body Mass Index, OME = oral morphine equivalents
Continuous data reported as median value with interquartile range
4. MODULATING CHOLANGIOCARCINOMA’S TUMOR MICROENVIRONMENT ENHANCES RESPONSE TO IMMUNE CHECKPOINT BLOCKADE

L Diggs, B Heinrich, L Cui, C Ma, Q Zang, B Ruf, S Wang, S Wabitsch, T Greten

Presenter: Laurence Diggs MD | National Institutes of Health

**Background:** Intrahepatic cholangiocarcinoma (iCCA) carries a very poor prognosis due to a typically late clinical presentation and a poor response to current therapeutics. iCCA’s tumor microenvironment (TME) has been shown to be immunosuppressive. While these tumors commonly express PD-1 and PD-L1, the response to immune checkpoint inhibitors (ICI) is poor. We hypothesized that modulating the TME by stimulating antigen-presenting cells (APCs) can improve response to ICIs. Specifically, stimulating CD40, a known receptor on all APCs, can drive increased effector cell cytotoxicity when combined with ICI.

**Methods:** We treated tumor bearing C57BL/6 mice with a CD40 agonistic antibody, an anti-PD1 antibody, and the combination (CD40/PD1) to compare treatment response. We used three different mouse models including subcutaneous and orthotopic injections of SB1, an established iCCA cell line as well as hydrodynamic tail vein injection of the YAP and AKT plasmids. Mice were then treated for three weeks with a CD40 agonist (2.5μg/g) weekly, an anti-PD-1 (10μg/g) weekly or the combination starting on post-tumor inoculation day five. Tumors were measured, weighed and evaluated histologically for differences between treated and untreated mice. Tumors were histologically proven iCCA (CK7 +, CK19+, HNF4α−). Immunohistochemical (IHC) staining characterized the TME including lymphocytes (CD4&CD8 T cells, B cells), myeloid cells (macrophages, dendritic cells), as well as PD-1 and CD-40 expression. Flow cytometric analysis of lymphoid and myeloid cell populations including activation status was performed. qPCR allowed for the identification of the cytokine mediators of treatment response. Finally, CD4, and CD8 T cell depletion was undertaken to identify effector cells.

**Results:** In subcutaneous, orthotopic, and plasmid models, mice treated with anti-PD-1 alone did not demonstrate significantly (p>0.05) lower tumor burden. Mice did exhibit a response to monotherapy with a CD40 agonist (p<0.05). When these agents were combined (CD40/PD1) however, a significantly greater reduction in tumor burden was seen (p<0.05) (Figure 1). IHC confirmed iCCA with increased areas of necrosis and calcification in CD40/PD-1 in the liver tumor tissue of treated mice. Flow cytometry demonstrated increased CD4+ and CD8+ T cells presence and activation as well as increased activation of myeloid cells in CD40/PD-1 treated mice. qPCR revealed increased presence of IL-2, TNF, iNOS, and Granzyme B within the tumor tissue and lymphocytes of mice treated with CD40/PD-1. T cell depletion demonstrated reduced efficacy of treatment with CD8 depletion and complete loss of efficacy of treatment with CD4 depletion (p<0.05).

**Conclusion:** In conclusion, modulation of the TME by CD40-mediated activation of APCs in iCCA appears to activate T cells and significantly enhances response to anti-PD-1 therapy. This process appears to be mediated both by CD4+ and CD8+ T cells. These findings offer a potential alternative to current cytotoxic chemotherapy regimens.
Background: Cholangiocarcinoma (CCA) is the second most common primary liver malignancy, with increasing incidence over the past decade. Currently, surgical resection offers the only curative treatment for this devastating disease. However, the prognosis remains poor, with a 5-year overall survival of as low as 10%, in part due to high rates of unresectability at presentation, recurrence, and poor response to conventional systemic therapy. Histologically, CCA is characterized by a desmoplastic stroma and robust immune infiltrate, both of which contribute to the immunosuppressive features of the disease. Identifying new systemic therapies remains a significant unmet medical need. Unfortunately, few pre-clinical models exist for identifying and testing new targeted or immune-based therapies. Here we present our findings of the immune infiltrate in the human CCA tumor microenvironment (TME) as well as a spontaneous murine model that faithfully recapitulates human disease.

Methods: Histology and immunohistochemistry (IHC) staining for stromal and immune markers was performed on archival human CCA and adjacent normal liver tissue specimens. Mice with targeted hepatic KrasG12D activation and homozygous loss of p53 (KPPC) were fed chow with 5-Diethoxycarbonyl-1,4-dihydrocollidine (DDC) for 4 weeks to induce liver inflammation associated with development of CCA. Disease onset and progression of liver tumors were tracked with high frequency ultrasonography (US). KPPC hepatic tumors and normal livers from littermate controls were formalin fixed-fixed and snap frozen for histological and gene expression studies. Bone marrow, spleen, peripheral blood, CCA tumors and normal livers from littermate controls were dissociated into single cell suspensions for immune phenotyping by flow cytometry analysis.

Results: Digital IHC quantification of CD15 and CXCR2 on archival human CCA specimens demonstrated significantly elevated levels of CD15+CXCR2+ tumor infiltrating granulocytic myeloid derived suppressor cells (G-MDSC) compared to adjacent normal liver ($p = < 0.05$). In addition, the predominate CXCR2 ligand, CXCL5, was significantly elevated in CCA compared to normal adjacent liver tissue. In KPPC mice, hepatic tumors were characterized with a prominent desmoplastic reaction and abundance of CD45+ inflammatory leukocyte infiltrate consistent with human CCA. Flow cytometry analysis of KPPC tumors demonstrated that immunosuppressive myeloid cells, including granulocytic myeloid derived suppressor cells (g-MDSC), were the most prevalent tumor infiltrating leukocytes compared to normal controls ($p = < 0.0007$). qRT-PCR demonstrated significantly elevated levels of granulocyte-colony stimulating factor (G-csf) and ELR+ cytokines including Csf1, Cxcl1, Cxcl2, and Cxcl5 compared to normal littermate control ($p = < 0.0001$) suggesting CCA induces granulopoiesis. Accordingly, flow cytometric analysis revealed a marked elevation in the number of granulocytes in the bone marrow and peripheral blood of KPPC mice compared to normal littermate controls.

Conclusion: These data suggest CCA co-opts the ELR+ cytokine/CXCR2 axes to induce granulopoiesis, mobilization and recruitment of immunosuppressive G-MDSC to the TME. Targeted immunotherapy against these tumor infiltrating neutrophils can be tested in this pre-clinical model to better inform clinical translation.
Background: Hepatitis C Virus (HCV) is a common risk factor for the development of hepatocellular carcinoma (HCC). Although HCV treatment has dramatically changed the landscape for HCV management, its widespread use is limited by its high cost. Given this potential obstacle, our aim was to assess barriers to receiving HCV treatment and the impact of HCV treatment on survival in patients with concurrent HCC treated at safety-net hospitals compared to academic referral centers.

Methods: Patients in the US Safety-Net Collaborative Database (2012-2014) with HCV and primary, non-metastatic HCC were included. The collaborative consists of five large safety-net hospitals and their academic referral center counterparts. Primary and secondary outcomes were overall survival (OS) and recurrence-free survival (RFS) based on HCV treatment status.

Results: Of 941 patients who had HCV-induced cirrhosis, median age was 60 years (IQR 56-64), 78% were male (n=734), 57% received care at an academic referral center (n=533) and 43% at a safety-net hospital (n=408). 25% received HCV treatment (n=245), while 74% did not (n=696). Among those who received HCV treatment, 76% of patients received care at an academic referral center (n=186) while 24% received care at a safety-net hospital (n=59). 6% underwent resection (n=54), 17% liver transplant (n=163), 50% liver-directed therapy (radiofrequency ablation, transarterial chemoembolization, Y90, and/or radiation therapy; n=473), 7% received chemotherapy (n=60), and 20% received no HCC treatment (n=191). Median follow-up was 37 months. For all patients, HCV treatment was associated with improved median OS compared to no HCV treatment (70 vs 21 months, p<0.01; Figure 1A). This association persisted across clinical stages I, II, III, and IVa (all p<0.01) and all HCC treatment modalities (all p<0.01). On multivariable Cox regression, accounting for age, insurance type, treatment facility type, MELD score, clinical stage, and HCC treatment type, HCV treatment was still associated with improved OS. In a subset analysis for patients who underwent complete tumor extirpation (surgical resection or liver transplant), patients who received HCV treatment had improved median RFS compared to those who did not (91 vs 80 months, p=0.03; Figure 1B). On multivariable analysis, factors associated with not receiving HCV treatment included Black race, uninsured status, and treatment at a safety-net hospital (all p<0.03). When this patient demographic did receive HCV treatment, however, the degree of improvement in survival was similar regardless if treated at an academic referral center (5-yr OS: 56 vs 30%, p<0.01; Figure 1C) or a safety-net hospital (5-yr OS: 52 vs 23%, p<0.01; Figure 1D).

Conclusion: HCV treatment for patients with HCC portends improved survival and oncologic outcomes, irrespective of clinical stage, HCC treatment modality, or type of treatment facility. Despite this, given its high cost and associated barriers, a minority of patients treated at safety-net hospitals receive HCV treatment. Efforts must be directed towards removing obstacles that prevent this vulnerable patient population from receiving the standard of care treatment for HCV with concurrent HCC.
Figure 1. Overall survival by HCV treatment for all patients (Panel A), recurrence-free survival by HCV treatment for surgical patients (Panel B), overall survival by HCV treatment at an academic referral center (Panel C), and overall survival by HCV treatment at a safety-net hospital (Panel D).
7. PRESENCE OF TRANSITIONAL CIRCULATING TUMOR CELLS FOLLOWING RESECTION IS ASSOCIATED WITH WORSE SURVIVAL IN PATIENTS WITH DELAYED INITIATION OF ADJUVANT THERAPY

A Hasanain, AA Javed, F van Oosten, G Gemenetzis, VP Groot, D Ding, JA Teinor, MJ Wright, J Yu, JL Cameron, MJ Weiss, WR Burns, RA Burkhart, L Zheng, J He, CL Wolfgang

Presenter: Alina Hasanain MD | Johns Hopkins University School of Medicine

Background: Outcomes in patients with pancreatic ductal adenocarcinoma (PDAC) remain poor and are predominantly driven by aggressive systemic disease. Despite improvements in treatment modalities, factors such as delay in the initiation of adjuvant therapy can still affect outcomes. Additionally, studies have reported that the presence and characteristics of circulating tumor cells (CTCs) are associated with outcomes. The aim of the current study was to assess whether CTC characteristics are associated with the impact of a delay in initiation of adjuvant therapy on patient outcomes.

Methods: A retrospective study was performed on patients with PDAC enrolled in the prospective CLUSTER trial (NCT02974764) on CTC dynamics at the Johns Hopkins Hospital. CTCs were isolated based on size (ISET; Rarecells) from peripheral blood and counted and characterized using immunofluorescence. All patients who received adjuvant therapy were included. A delay in receipt of adjuvant therapy was defined as initiation >2 months after surgical resection. Clinicopathological features, CTC characteristics, and outcomes of these patients were analyzed.

Results: A total of 84 patients were included in the study, of whom 43 (51.1%) experienced a delay in initiation of adjuvant therapy. Both cohorts of patients (delayed vs. timely initiation of adjuvant therapy) were well balanced in terms of their clinicopathological features (All p-values >0.05). In patients with timely initiation of therapy, the only factor independently associated with DFS on multivariable analysis was the receipt of neoadjuvant therapy (Hazard ratio [HR]: 2.38, 95% Confidence interval [95%CI]: 1.09-5.20, p=0.029). Postoperative transitional CTCs (mCTCs) positivity was not associated with DFS in this population (p=0.633). Contrastingly, in patients with a delay in initiation of adjuvant therapy, factors independently associated with poorer DFS on multivariable analysis included the presence of poorly differentiated or undifferentiated tumors (HR: 1.77, 95%CI: 1.13-2.76, p=0.013) and postoperative mCTCs positivity (HR: 2.72, 95%CI: 1.02-7.27, p=0.046). In patients with a delay in initiation of adjuvant therapy, those with postoperative mCTCs positivity had worse DFS compared to those without mCTCs (median DFS: 16.7 vs. 10.1 months, p=0.002) (Figure).

Conclusion: Postoperative mCTCs positivity was associated with poorer DFS only in patients experiencing a delay in initiation of adjuvant therapy. This study is the first to propose a potential biological mechanism for the previously established observation that a delay in initiation of adjuvant therapy results in worse survival. Future mechanistic studies are required to validate these findings and explore the underlying mechanisms involved.
Background: Early intrahepatic recurrence (EIR) occurs within 2-years and is the clinical manifestation of micrometastases in the remnant liver following surgical resection. 30-50% of patients undergoing hepatectomy for hepatocellular carcinoma (HCC) develop EIR. Despite improved multiphase cross-sectional imaging and updated LI-RADS criteria, current diagnostic modalities have poor sensitivity for small HCC lesions which contribute to a high EIR rate. Therefore, diagnostic modalities with higher sensitivity are needed. Our group developed an antibody against glypican-3 (GPC3), a cell-surface protein that is expressed in HCC, which specifically identified tumors with zirconium-89 (89Zr) immuno positron emission tomography (PET). The objective of this study was to validate 89Zr-\(\alpha\)GPC3 immuno-PET, determine its accuracy in identifying small HCC lesions and measuring tumor size in an orthotopic xenograft HCC model.

Methods: A murine orthotopic xenograft model of HCC was generated by subcapsular injection of luciferase-transfected human hepG2 cells, which natively express GPC3. After verifying tumor development with bioluminescent imaging, serum alpha-fetoprotein (AFP) concentration, an established surrogate for tumor size in our model, was serially measured to monitor tumor growth. Animals were then injected with 89Zr-\(\alpha\)GPC3 and imaged using the Inveon PET/CT scanner (Siemens). PET images were reconstructed and localizations of increased intensity in the midline upper abdomen were classified as tumors. Gross tumor volume (GTV) was measured by a combination of fixed thresholding and manual segmentation methods. For fixed threshold method, the minimum threshold intensity was set at 40% of the maximum signal intensity at the tumor and liver-parenchymal interface. All segmentation was performed by a user blinded to experimental conditions of each mouse.

Results: 58 tumors were imaged by immuno-PET with a mean GTV of 0.26cm³ (SD 0.39cm³), corresponding to a spherical tumor diameter of 8mm and a mean serum AFP of 235,724 ng/mL (SD 291,438). The smallest GTV was 0.001cm³, corresponding to a spherical tumor diameter of 1.2mm. The largest GTV was 1.54cm³, corresponding to a spherical tumor diameter of 14.4mm. GTV measurements accurately correlated with serum AFP (Figure 1) confirming accuracy of tumor volume measurement. 30% of tumors measured were less than 5mm in diameter, the lower limit of sensitivity for magnetic resonance imaging for HCC.

Conclusion: Immuno-PET using 89Zr-\(\alpha\)GPC3 specifically identifies sub-centimeter HCCs and accurately measures tumor volume in a GPC3 expressing orthotopic tumor model. With improved sensitivity and specificity of HCC detection using this technology, the EIR rate may be reduced and selection of patients who would benefit from upfront surgery versus neoadjuvant therapy may be determined.
9. EPIDURAL ANALGESIA IS ASSOCIATED WITH PROLONGED LENGTH OF STAY AFTER OPEN HPB SURGERY IN OVER 27,000 PATIENTS
L Kone, VK Maker, M Banulescu, AV Maker
Presenter: Lyonell Kone MD, MHS | University of Illinois at Chicago

Background: The impact of epidural analgesia (EA) on post-operative morbidity and length of stay after HPB surgery remains to be determined. These specific outcomes have been highlighted by the implementation of multiple enhanced recovery pathways (ERAS) that focus on minimizing opioid use and length of stay. We hypothesized that epidural analgesia (EA) in the current environment may be associated with length of stay and other post-operative outcomes.

Methods: Demographic characteristics, perioperative, intraoperative, and postoperative data were captured from the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) 2014 to 2017 for patients undergoing open hepatic and pancreatic (HPB) surgery. Potential confounders were adjusted for in stepwise linear and logistic regressions, and propensity score-matching models. The primary outcome was length of stay (LOS). Secondary outcomes included post-operative morbidity and disposition.

Results: Over a four-year period, 27,218 patients underwent major open HPB surgery, of which 6,048 (22%) received EA. There was an increase in the use of EA across the years (from 2014-2017 = 19.3%, 21.5%, 22.7%, 25.5%, p=0.001). On multivariate analysis (MVA) and propensity score matching (PSM) to control for differences between groups in baseline characteristics across 46 variables (14 pancreatectomy-specific and 9 hepatectomy-specific variables), EA was associated with an increased LOS amongst pancreatectomy (MVA: Coef=0.57, p<0.001; PSM: ATET=0.40, p=0.01) and hepatectomy patients (MVA: Coef=0.48, p<0.001; PSM: ATET=0.44, p<0.001), increased discharge to rehabilitation (MVA: OR=1.55, p=0.003; PSM=ATET: 0.02, p=0.003) and time to drain removal for pancreatectomy patients (MVA: Coef=0.84, p<0.001; PSM: ATET=0.74, p=0.006). Differences in wound dehiscence, cardiac arrest, urinary tract infection and sepsis on multivariate analysis did not persist after PSM. Furthermore, there were no differences in DVT, PE, MI, pneumonia, superficial/deep/organ-space surgical site infections, or mortality between the groups.

Conclusion: Epidural use after HPB surgery has been significantly increasing over time and is associated with an increase in length of stay without affecting morbidity or mortality. Further, EA is associated with increased rates of discharge to rehabilitation and time to drain removal after pancreatectomy. Further studies evaluating the etiology of these outcomes are necessary and warranted to improve outcomes.
### Table 1. Comparison of outcomes with EA stratified by surgery type

#### Pancreatectomy (n=16,740)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR/Coef</th>
<th>P-value</th>
<th>ATET</th>
<th>P-value</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Multivariate regression</td>
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<td>PSM (1:1)</td>
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<tr>
<td>LOS</td>
<td>0.57 (coef)</td>
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<td>DVT</td>
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<td>PE</td>
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<td>0.004</td>
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#### Hepatectomy (n=10,478)

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<th>Outcome</th>
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<th>ATET</th>
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10. AN ONLINE CALCULATOR TO PREDICT RECURRENTNESS AFTER HEPATECTOMY FOR COLORECTAL LIVER METASTASIS: REFLECTING THE NEW ERA OF GENETIC AND BIOLOGICAL FEATURES


Presenter: Amika Moro MD | The Ohio State University

Background: The risk of recurrence after hepatectomy for colorectal liver metastasis (CRLM) remains high. The objective of the current study was to develop a novel online calculator to estimate the risk of CRLM recurrence using pathological, genetic, and morphologic tumor characteristics.

Methods: Patients who underwent hepatectomy for CRLM between 2001-2018 were identified from a multi-institutional international database. A prognostic model was developed in the training set and validated using an external cohort. Patients were categorized into three risk groups (low, intermediate, and high-risk) based on the model score. An online calculator to estimate 1, 3, 5-year recurrence free survival (RFS) was developed and compared with the clinical risk score (CRS) using Harell’s c-index.

Results: Among 1,125 patients who underwent CRLM resection, median tumor number was 2 (IQR, 1-3) and median tumor size was 3.0cm (IQR, 2.0-5.0). Median CEA level was 9.9 ng/mL (IQR, 3.8-44.8), while a subset of patients presented with synchronous disease (n=792, 70.4%). On pathology, one-third of patients had mtKRAS (n=343, 30.4%), while 69.6% (n=782) had wtKRAS. Overall 1-, 3-, 5-year RFS was 61.1%, 33.9%, and 28.1%, respectively. The CRS performed relatively poorly with a c-index of 0.61. In turn, an on-line calculator based on a prognostic model that included clinical, pathological, KRAS status, as well as response to chemotherapy was developed (https://medicalcal.shinyapps.io/CRLM_RFS/) (Figure). The 5-year RFS among low, intermediate, and high-risk group patients was 43.1%, 16.1%, and 3.3%, respectively (log-rank p <0.001). The new prognostic model performed better than the CRS among all patients with CRLM (c-index: 0.71 vs. 0.61), as well as among patients who had wtKRAS (c-index: 0.68 vs. 0.62) or mtKRAS (c-index: 0.73 vs. 0.61) tumors. External validation of the on-line prognostic calculator revealed good to very-good accuracy (c-index: 0.66).

Conclusion: The traditional CRS performed poorly in stratifying patients relative to RFS. A novel online calculator that incorporated patient, tumor, KRAS status, as well as response to chemotherapy was more accurate in stratifying patients relative to RFS. These data highlight the importance of incorporating clinical and genetic information in estimating prognosis among patients with CRLM.
# Recurrence free survival after hepatectomy for CRLM

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<tr>
<td><strong>CEA at diagnosis (ng/ml):</strong></td>
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<tr>
<td><strong>Number of CRLM:</strong></td>
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<tr>
<td><strong>Site of primary tumor:</strong></td>
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<tr>
<td><strong>Synchronous liver metastasis:</strong></td>
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<tr>
<td><strong>Lymphnode metastasis of primary tumor:</strong></td>
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<tr>
<td><strong>KRAS status:</strong></td>
<td>Wild type</td>
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<tr>
<td><strong>Chemotherapy for CRLM:</strong></td>
<td>No</td>
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</tbody>
</table>

1 year RFS probability: 29.7%
3 year RFS probability: 4.3%
5 year RFS probability: 2.7%

Your risk group is: High risk group

Recurrence free survival according to risk groups defined by the model

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**The Ohio State University**

**Wexner Medical Center**
Background: Previous studies demonstrated the effects of Intestinal microbiota composition on physiologic and pathologic processes in the liver, such as steatosis and steatohepatitis. Our aim was to study the effect of the intestinal microbiota composition on the process of liver regeneration (LR) using a model of fecal microbiota transplantation (FMT) prior to partial hepatectomy (PH).

Methods: We used the 70% PH model in mice to induce LR. LR was assessed using liver to mouse weight ratio, KI67 staining, and RT-PCR for Cyclin D1. The intestinal microbiome was manipulated by aggressive antibiotic treatment followed by FMT. Normal, as well as obese mice received FMT by gavage from normal and obese mice, as well as vehicle saline.

Results: We studied the effects of pre-operative antibiotics on LR using a combination of four wide spectrum oral antibiotics, and demonstrated that LR was not affected by the antibiotic treatment. Next, we studied effects of antibiotic treatment followed by FMT and PH on normal mice. We showed that FMT from healthy normal mice, compared to vehicle resulted in improved LR (Fig. 1 A), and that FMT from obese mice was associated with increased postoperative mortality (45% vs. 8%). Next, we studied the effects of antibiotic treatment followed by FMT and PH on obese mice. We showed that obese mice receiving FMT from obese mice had decreased LR (Fig. 1 B).

Conclusion: LR is affected by microbiome composition, and can be manipulated by FMT. Whereas microbiota transfer from healthy donor mice enhances LR, microbiota transfer of dysbiotic microbiota from HFD donor mice impairs LR, following PH.
Liver regeneration is enhanced in mice treated with pre-surgical FMT using healthy donor and impaired by fecal dysbiotic (obese) donor. Mice (C57BL6) were pre-surgically (PH) treated for 2 weeks with Aib-containing water followed by microbiome transplantation by oral gavage. Five days after treatment mice were operated. FMT was administrating in (A) normal recipients mice and (B) obese recipients mice. The percentage of the remaining liver to body weight ratio was evaluated at day four after surgery (left), quantification of Ki-67 positive nuclei of hepatocytes after PH (middle) and qRT-PCR showed relative messenger RNA expression in liver - Cyclin D1 fold-change levels compared to vehicle (right). *p < 0.05.
12. SURGICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA PATIENTS WITH PORTAL VEIN THROMBOSIS: A UNITED STATES SAFETY NET COLLABORATIVE ANALYSIS


Presenter: Emily Ryon MD, MPH | University of Miami Miller School of Medicine

Background: Although consensus guidelines generally discourage surgical management in patients with hepatocellular carcinoma (HCC) and portal vein thrombosis (PVT), recent series from Asia have challenged this paradigm. We evaluated factors associated with selection of any surgical management (ASM; i.e., resection and/or transplantation), as well as its association with overall survival (OS), in HCC patients with PVT in a large North American cohort.

Methods: All patients with non-metastatic HCC and radiographically-confirmed PVT from the five-center US Safety Net Collaborative database (2012-14) were included. Multivariable analysis identified demographic and clinicopathologic factors associated with receipt of ASM. Cox proportional hazards model assessed factors associated with ASM and OS.

Results: Of 1910 HCC patients, 277 (14.5%) had locoregional disease and radiographically-confirmed PVT. In this study-eligible cohort, 93 (33.6%) underwent liver-directed therapies (Y90 radioembolization, n=41; trans-arterial chemoembolization, n=52) and 85 (30.7%) received tyrosine kinase inhibitor therapy. Twenty-three patients (8.3%) underwent ASM (11 [47.8%] transplantation, 7 [30.4%] major hepatectomy, and 4 [17.4%] minor hepatectomy). In the perioperative period, 7 (30.4%) experienced any complication, 3 (13.0%) required additional procedures, 6 (28.6%) were readmitted within 90 days, and there were no 30-day mortalities. Of patients undergoing hepatectomy, 90.9% were R0 resections. On multivariable analysis, independent predictors of ASM were younger age (OR 1.22, p=0.001), hepatology consultation within 1 year of diagnosis (OR 14.2, p=0.006) and lower MELD score (OR 1.51, p=0.004). Notably, race/ethnicity, presence of comorbidities, treatment at an academic center, and receipt of targeted and/or liver-directed therapies were not significantly associated with ASM. At a median follow-up of 55.9 (IQR 16-64) months, OS was significantly longer for patients selected for ASM compared with non-ASM patients (median not reached vs. 5 months, p<0.001). When controlling for demographics, comorbidities, pre-existing liver disease, and stage at presentation, ASM was independently associated with improved OS (HR 0.53, 95% CI 0.29-0.96, p=0.035, Figure).

Conclusion: In a large North American multi-institutional cohort, a minority of HCC patients with PVT were selected for ASM. Resection or transplantation results in a significant improvement in OS and may have a role in multimodality management of patients with PVT. Factors associated with receipt of ASM in this heavily pre-treated population suggest careful selection.
Figure 1. Improved adjusted* overall survival in HCC patients with portal vein thrombosis undergoing any surgical management

* Cox proportional hazards model controlling for age, gender, race, ethnicity, BMI, insurance status, location of diagnosis, functional status, smoking, alcohol use, treatment of HCV, cirrhosis, MELD score, Child-Pugh Class, lymph node involvement, number of tumors, receipt of liver targeted therapies and systemic chemotherapy.
13. BIOMARKERS AFP IN COMBINATION WITH AFP-L3 AND DCP PREDICTS TUMOR PROGRESSION IN TREATMENT NAÏVE HCC PATIENTS
K Nunez, T Sandow, P Thevenot, A Cohen
Presenter: Kelley Nunez PhD | Ochsner Health System

Background: Hepatocellular carcinoma (HCC) treatment with locoregional therapy (LRT) is standard process to downstage or maintain lesions within Milan Criteria. In this study, we retrospectively analyzed early-stage HCC patients undergoing de novo LRT and monitored both recurrence-free survival and intention-to-treat (ITT) survival. We also prospectively monitored a subset of early-stage HCC patients to determine whether additional HCC biomarkers would aid in predicting ITT survival compared to α-fetoprotein (AFP) alone.

Methods: All studies were IRB-approved at our institution. A retrospective review of HCC patients transplanted from June 2011 – Feb 2019 that underwent DEB-TACE was performed with patients monitored for 5 year recurrence. In the ITT cohort, HCC patients undergoing de novo DEB-TACE from Aug 2015 – May 2019 were reviewed. Blood was collected from a subset of the ITT cohort (n=52) immediately prior to LRT. Plasma was used to measure HCC biomarkers (AFP, des-carboxy prothrombin (DCP), and Lens culinaris agglutinin-reactive α-fetoprotein (AFP-L3)) in samples with the TASWako i30 autoanalyzer. ITT endpoint included patients that received liver transplantation or dropout due to tumor progression.

Results: In the retrospective transplanted cohort, 268 treatment-naïve patients were analyzed with 75% male and main etiology of Hepatitis C (58%). Recurrence free survival was significantly lower in patients that presented with AFP > 100 (P=0.01). In the ITT cohort, 160 treatment-naïve HCC patients were analyzed with 71% male and 65% Hepatitis C. Milan Criteria and AFP elevation alone was not predictive ITT survival, however patients with AFP > 100 had significantly lower ITT survival. A subset of the ITT cohort was prospectively monitored with blood collections. Demographic comparisons between two revealed only significant differences in sodium and bilirubin levels. Univariate analysis revealed patients with tumor progression had larger lesions (P<0.0001), cumulative lesion size (P<0.0001), and higher HCC biomarkers AFP (P=0.39), AFP-L3 (P=0.002), and DCP (P=0.005). ITT survival was significantly lower in patients presenting with elevated single biomarkers [AFP >100 (P<0.0001), AFP-L3 (P<0.0001), and DCP (P<0.0001)], primary lesion >3cm (P<0.0001), and cumulative lesion size >3cm (P<0.0001). Analysis of patients stratified by HCC biomarkers revealed patients presenting with AFP elevation and an additional biomarker had worse ITT survival and were at greater risk of waitlist dropout.

Conclusion: AFP alone can identify patients at risk of waitlist dropout with higher risk of recurrence post transplant. However, the addition of AFP-L3 and DCP biomarkers can identify a patient population prior to LRT intervention at risk of tumor progression from the waitlist.
14. INTERNATIONAL MANAGEMENT OF DISAPPEARING COLORECTAL LIVER METASTASES SURVEY
LG Melstrom, SG Warner, P Wong, V Sun, M Raoof, G Singh, Y Fong, TJ Hugh
Presenter: Laleh Melstrom MD, MSCI | City of Hope Cancer Center

Background: Liver metastases present in up to 50% of patients diagnosed with colorectal cancer. Appropriate resection offers improved survival and potential for cure. Chemotherapy response rates have markedly improved leading to the occurrence of “disappearing” liver metastases. The management of “disappearing” colorectal liver metastases (dCRLM) is controversial. The aim of this work is to assess the management of dCRLM as determined by a survey of an international body of hepatobiliary surgeons.

Methods: A survey was designed and tested for item relevance and readability, and a content validity index (CVI) was determined based on review by 10 content experts. IRB exemption was obtained and the survey was distributed to members of the Americas Hepatobiliary Association and the Australian and New Zealand Hepatic, Pancreatic and Biliary Association.

Results: There were 85 respondents to the survey. The majority of respondents were within 15 years of training completion (62.73%), practiced in an academic setting (73.87%) and devoted more than 50% of their practice to hepatobiliary surgery (67.78%). Nearly all had completed fellowship training primarily in Hepatobiliary (67%), Surgical Oncology (43%) and Transplant Surgery (33%). There was representation from North America (68%), South America (18%), Europe (4%) and Australia/New Zealand (10%). Intraoperative ablation is offered in 95% of the responders’ institutions and is performed by the surgeon (45%), the interventional radiologist (15%) or both (34%). The preferred ablation modalities are microwave (67%) and radiofrequency (31%). Most surgeons utilize Computed Tomography (40%) or Magnetic Resonance Imaging (48%) for preoperative planning. The decision for preoperative chemotherapy is always a combined multidisciplinary decision in 63% of cases and up to the surgeon in 13%. Nearly all surgeons have experienced dCRLM (98%) and 61% of surgeons have waited a few months to assess for a durable response prior to definitive surgical/ablative therapy. Interestingly, more than ¼ surgeons surveyed (27%) place fiducials for lesions less than 1-cm prior to neoadjuvant chemotherapy to help identify lesions in the operating room; of those that don’t, 46% (32) believe it is not useful. Many surgeons rely on preoperative PET scan to determine if dCRLM are still viable (28%). Nearly all surgeons insist on recent imaging (< 6 weeks) prior to liver resection. Intraoperatively, 97% of surgeons perform ultrasound, and 79% report performing intraoperative liver ablation themselves. Surgeons report that the primary challenges of lesion identification include steatosis, surgeon ultrasound experience, small size of the treated CRLM, and lesion location. When a tumor has “disappeared,” 50% of respondents elect for observation and 28% resect if the dCRLM is superficial. Of those that elect for observation, 89% believe it is still possible to treat effectively if the CRLM grows on surveillance imaging.

Conclusion: While surgical management of dCRLM varies widely, nearly all surgeons use intraoperative ultrasound and mandate recent preoperative imaging. Interestingly, nearly half of the respondents elect for observation with the belief that there remains an opportunity to re-address these lesions in the future.
Background: Systemic chemotherapy is the primary treatment for patients with metastatic solid malignancies, and response to chemotherapy has emerged as a universal prognostic marker for patients with different cancer types, across all stages, and beyond other important predictors of survival. However, response to chemotherapy is extremely variable and unpredictable, and the heterogeneity in the physical delivery of anticancer agents from systemic circulation into solid tumors - as a plausible explanation - remains remarkably understudied. We sought to evaluate chemotherapy concentration at the tumor-site and its association with response to therapy.

Methods: We implemented a validated mathematical tumor perfusion model in patients with colorectal liver metastasis (CLM) having received chemotherapy prior to curative-intent liver resection. Using multivariate correlation analysis including patient and tumor characteristics, tissue perfusion/diffusion data, and chemotherapy treatment information (BSA-specific dose and cycles), we developed a mathematical formula to estimate chemotherapy concentration at the tumor-site. The primary outcome of interest was response to chemotherapy in resected specimens – measured using the gold standard: tumor regression grade (TRG). The differential response to therapy (TRG 1-5) was examined in relation to the systemic and tumor-site chemotherapy concentration. Regression analysis was done using the Levenberg-Marquardt algorithm. The performance of the model in terms of its predictive ability was examined for accuracy, sensitivity and specificity, and the overall discrimination (AUC – c-statistic).

Results: A total of 33 patients with CLM, meeting inclusion criteria, and with all information required for model development, represented the study sample (2016-2018). Median age was 57 and 60% of patients were male. Most patients received FOLFOX-based chemotherapy (76%), with a median number of 4 preoperative cycles. We found the average plasma concentration of chemotherapy to be essentially equivalent (minimal variability) across patients exhibiting different TRGs (P > 0.05), while the tumor-site concentration showed a quadratic decline when moving from TRG = 1 (best response) to TRG = 5 (no response) (P < 0.001). The chemotherapy concentration at the tumor-site was significantly lower than the observed plasma concentration and dropped significantly between patients with complete response (TRG = 1) and those with no response (TRG = 5), by a factor of ~4.8, while the plasma concentration remains stable across TRG groups (Figure). The model was able to predict TRG based on the mathematical estimation of the chemotherapy concentration at the tumor-site with an accuracy of 85%, sensitivity of 83%, specificity of 85% and an overall excellent discrimination (AUC/c-statistic=0.88 with the tumor-site concentration threshold of 0.51 μg/ml⁻¹).

Conclusion: We found, despite similar concentration of chemotherapy in the systemic circulation across patients, TRG variations were driven and predicted by differences in tumor perfusion and chemotherapy concentration at the tumor-site, as calculated by a validated tumor perfusion mathematical model. These findings represent fundamental groundwork to support a new paradigm for individualized care of patients with hypovascular tumors, including precise prediction of response to therapy and development of novel models for chemotherapy delivery.
**Background:** Measurement of hepatic vein pressure gradient (HVPG) is frequently used to evaluate portal hypertension in high-risk patients prior to liver resection, specifically in patients with cirrhosis. Von Willebrand Factor-antigen (vWF-Ag) has been described to closely correlate with HVPG measurement and clinical outcome in patients suffering from cirrhosis. We have recently demonstrated vWF-Ag to be a significant predictor for poor postoperative outcome in regards to complications and liver dysfunction (LD). However, direct comparative analyses and long term outcomes in context to these parameters has not been evaluated so far.

**Methods:** HVPG and vWF-Ag were evaluated prior to liver resection in 72 patients with hepatocellular carcinoma (HCC). Postoperatively overall survival (OS) and disease-free survival (DFS) were assessed as well as severe morbidity and LD. Previously defined cut offs were used to define risk groups within the cohort.

**Results:** While both a cut-off for HVPG at 5 mmHg and a cut-off for vWF-Ag at 182% could identify patients at risk for severe morbidity (p=0.038, respectively), only vWF-Ag was able to significantly predict LD prior liver resection (p<0.001). Further, Kaplan-Meier analysis revealed that vWF-Ag allowed stratification of patients in regards to OS (median OS vWF-Ag < 182%=95.6 months vs. median OS vWF-Ag≥182%=40.1 months, p=0.003). In clear contrast, HVPG did not show an association with OS (p=0.486). Intriguingly, vWF-Ag was also able to predict DFS in our cohort (median DFS vWF-Ag < 182%=950 days vs. median DFS vWF-Ag≥182%=648 days, p=0.011), while DFS was not associated with preoperative HVPG levels (p=0.742).

**Conclusion:** These findings clearly demonstrate that vWF-Ag is a valuable predictor of postoperative outcome after liver resection in high risk patients such as patients suffering from HCC. This non-invasive parameter of portal hypertension is not only equally effective but superior in terms of risk assessment as compared to the invasive and costly HVPG assessment. The close association with long term outcome seems to not only be caused by vWF-Ag association with postoperative LD but also its association with oncological outcome such as DFS after HCC resection. Thus, vWF-Ag presents a non-invasive and easily assessible tool for risk assessment in HCC patients undergoing liver resection.
17. IS IT TIME TO MOVE BEYOND FEAR OF CELL SALVAGE AND MISCONCEPTIONS ABOUT METASTASIS: EVALUATING THE FEASIBILITY OF AUTOLOGOUS BLOOD TRANSFUSION FOR PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA

N Goel, A Rhim, B Schrope, K Sugahara, J Chabot, M Kluger

Presenter: Neha Goel MD | Columbia University

Background: Allogeneic transfusions are more expensive and have been found to increase perioperative morbidity, mortality, and decrease recurrence-free and overall survival. Operative blood loss can be cell-salvaged for immediate transfusion by recovery devices widely used for noncancer operations. Transfusion rates during pancreatic surgery are as high as 75% and recent analysis of a nationally representative dataset found 26.4% of patients undergoing pancreatic surgery received red blood cells (RBCs). Recovery devices are not used during pancreatic surgery due to a belief, in the absence of data, that circulating tumor cells (CTCs) will "seed" the patient and cause metastases. Though intuitively reasonable, this belief is belied by our modern understanding of metastasis biology. In particular, there is evidence that CTCs continuously circulate in patients with PDAC and may be present even before the diagnosis of an overt tumor. There is no distinction between these cells and any that might be transfused back into the patient. This study is the first to compare PDAC CTCs in the systemic circulation prior to surgery, at the time of surgery, and in cell-salvaged filtered blood collected to evaluate whether recovered blood contains a greater concentration of CTCs.

Methods: We conducted a prospective study of 50 patients with PDAC who underwent a pancreaticoduodenectomy, an Appleby procedure, or a total pancreatectomy at a high-volume academic center. Demographic, clinical, treatment, operative [type of surgery and average estimated blood loss (EBL)], and intra-operative and post-operative transfusion data were collected. Pre-operative systemic, intra-operative systemic, and cell salvaged filtered blood was collected to evaluate CTCs using GEDI-captured PDAC-specific nucleated cells. Salvaged intraoperative blood was filtered through either a leukoreduction filter or a 40 µm microaggregate filter. Wilcoxon matched-pairs signed-ranks test was used to compare CTCs in systemic pre-operative, intra-operative systemic, and cell-salvaged filtered blood.

Results: Of 50 patients, median age was 67.5 and 29 (58%) were male (Table 1). Thirty-two (64%) had borderline or locally advanced disease and 26 (52%) received neoadjuvant treatment. Venous reconstruction was performed in 32% of patients. On final pathology, 2% were T1, 26% were T2, 52% were T3, and 16% were T4. Thirty-six (18%) had N1 disease and 32 (16%) had N2 disease. Median EBL was 1000ml and 32% were transfused POD 0 and 13 had transfusions POD 1-7. Variance in CTCs relative to systemic pre-operative CTCs was analyzed using Wilcoxon matched-pairs signed-ranks test and revealed no significant difference in the number of CTCs from systemic-intraoperative blood (p=0.8115) or from cell-salvaged filtered blood (p=0.8998).

Conclusion: This prospective study is the first to objectively evaluate and compare the number of CTCs in systemic pre-operative, systemic intra-operative, and cell-salvaged filtered blood. Given no significant difference in the number of CTCs in systemic pre-operative, systemic intra-operative, and cell-salvaged filtered blood, this study serves as a foundation to consider autologous transfusion during PDAC surgery given the deleterious effects of allogeneic transfusions. Further, multi-institutional studies need to be conducted to validate our finding.
Table 1: Demographics, clinical, treatment, transfusion, and circulating tumor cells for patients undergoing surgery for pancreatic ductal adenocarcinoma

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</tr>
<tr>
<td>Operation</td>
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<tr>
<td>Whipple</td>
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<tr>
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<tr>
<td>Resectability</td>
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<td>18</td>
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<td>Borderline/Locally Advanced</td>
<td>32</td>
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<td>Venous Reconstruction</td>
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<tr>
<td>No</td>
<td>34</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>Irreversible Electroportation</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45</td>
</tr>
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<td>Yes</td>
<td>5</td>
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<td>Frozen Margin</td>
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<td>N Stage</td>
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<td>Intra-Operative</td>
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<td>Estimated blood loss (ml)</td>
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<tr>
<td>PRBC Transfusion (ml)</td>
<td>0 (IQR 0,700)</td>
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<tr>
<td>Transfused POD#0</td>
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<td>Post-Operative</td>
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<tr>
<td>Additional Transfusions (7 days (ml))</td>
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</tr>
<tr>
<td>Transfused POD#1-7</td>
<td>13</td>
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<tr>
<td>Cell Salvage Reservoir, unprocessed (ml)</td>
<td>800 (IQR 600,1500)</td>
</tr>
<tr>
<td>Salvaged, processed (ml)</td>
<td>350 (IQR 350,700)</td>
</tr>
<tr>
<td>Circulating Tumor Cells</td>
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<td>Systemic, pre-op</td>
<td>1 (IQR 0,2)</td>
</tr>
<tr>
<td>Systemic, intra-op</td>
<td>1 (IQR 0,1)</td>
</tr>
<tr>
<td>Salvaged, filtered</td>
<td>1 (IQR 0,2)</td>
</tr>
<tr>
<td>Leukocyte Depletion Filter</td>
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<td>Leukoreduction filter</td>
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<tr>
<td>40 μm microaggregate filter</td>
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*variance in CTCs relative to systemic, pre-operative CTCs
18. PRELIMINARY RESULTS OF A PHASE IB CLINICAL TRIAL OF A NEOANTIGEN DNA VACCINE FOR PANCREATIC CANCER

D Cullinan, M McLellan, X Zhang, T Vickery, N Myers, M Sturmoski, M Ruzinova, J Hundal, C Miller, M Griffith, R Schreiber, K Lim, S Goedegebuure, W Hawkins, W Gillanders

Presenter: Darren Cullinan MD, MSCI | Washington University, St. Louis

**Background:** Neoantigens result from somatic mutations present in cancers but not normal tissue. Neoantigens appear to play an important role in cancer immunotherapies and represent an attractive target for cancer vaccines.

**Methods:** Following IRB and FDA approval, a phase Ib clinical trial testing the safety and immunogenicity of a neoantigen DNA vaccine in pancreatic cancer opened for enrollment (NCT03122106). Nonsynonymous mutations were identified using tumor/normal whole-exome sequencing, and gene expression in the tumor at the mRNA level was verified using cDNA-capture sequencing. Candidate neoantigens were identified and prioritized using the pVACSeq suite of computational tools. Patients who underwent surgical resection and completed adjuvant chemotherapy without recurrent disease received a neoantigen vaccine at monthly intervals for six months using an electroporation device. Peripheral blood for immune monitoring was drawn at enrollment and at each vaccination. The primary endpoint of safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v4. The secondary endpoint of immunogenicity was evaluated by IFN-g ELISpot analyses using peripheral blood mononuclear cells (PBMC) and synthetic peptides. Additional analyses were performed by rescuing PBMC from the ELISpot assay and then culturing with IL-2 for twelve-days.

**Results:** To date, fourteen patents have been enrolled. Six patients have withdrawn or become ineligible for vaccination, with the most common reason being progression on adjuvant therapy (n=3). Neoantigen vaccines have been produced for eight patients targeting an average of 13 candidate neoantigens per patient (range 5-20). Thus far, seven patients have received a total of 29 vaccines, with two patients completing the series of six vaccines. There have been zero adverse events of grade three or above with the most common side effect being pain at the injection site (grade I). The initial immune response monitoring for the two patients who have completed the series of vaccinations demonstrates successful generation of neoantigen-specific immune responses in both patients. Patient 8105-002 showed a doubling of the immune response from pre-vaccine levels to post-vaccine peak levels in five of the six pools of peptides (Figure 1a). IFN-g ELISpot testing following a twelve-day in vitro culture confirmed response to five of the twelve neoantigens included in the vaccine. Patient 8105-004 showed a doubling of immune response pre-vaccine levels to post-vaccine peak levels in two of five pools of peptides (Figure 1b). IFN-g ELISpot testing following a twelve-day in vitro culture confirmed response to two of the five neoantigens included in the vaccine.

**Conclusion:** In the first human studies of neoantigen vaccines for pancreatic cancer, neoantigen DNA vaccines appear safe in the adjuvant setting of pancreatic cancer. Initial immune monitoring demonstrates increased immune response following vaccination.
Figure 1

A  8105-002

B  8105-004
19. PATIENTS WITH DELETERIOUS GERMLINE MUTATIONS: A HETEROGENEOUS POPULATION FOR PANCREATIC CANCER SCREENING?
AM Roch, MH Al-Temimi, T Nguyen, MG House, NJ Zyromski, A Nakeeb, CM Schmidt, EP Ceppa
Presenter: Alexandra M. Roch MD, MS | Indiana University

Background: Many germline mutations are associated with an increased risk of pancreatic adenocarcinoma (PDAC). Screening at our institution is currently offered for mutation carriers or patients with at least one first-degree relative or two family members with PDAC. High-risk screening protocol includes complete history and physical examination, tumor markers (CA19-9 and CEA), and cross-sectional imaging (CT or MRI/MRCP with Gadolinium and Secretin enhancement), followed by semi-annual to annual clinic visits. Little data exists on the benefits of screening and surveillance for high-risk individuals with inherited genetic syndromes. Intraductal papillary mucinous neoplasm (IPMN) are well-established cystic precursors of PDAC. We hypothesized that patients with deleterious germline mutations in a pancreatic cancer susceptibility gene have a higher prevalence of IPMN.

Methods: All consecutive patients undergoing going surveillance at our Pancreatic Cyst and Cancer Early Detection Center from 2013 to 2019 were included in the present study. We analyzed the prevalence and risk factors for IPMN in this high-risk population. Prevalence was compared to historical data from extensive literature review.

Results: Of the 1166 patients in the surveillance program, 358 (31%) had a germline mutation and/or a strong family history of PDAC without a known mutation. Gender ratio was 3.5 in favor of women with a median age of 58 years, and a median follow-up of 2.7 years [range 1 month-6 years]. 201 patients (56%) were known to harbor a deleterious germline mutation, the most common being BRCA2 in 89 patients (25%). A total of 250 patients (70%) had a family history of pancreatic cancer. 132 patients had an IPMN (56%) and 8 had a PDAC (2%). The prevalence of IPMN was higher in the mutation carriers than in the general population (18% vs. 1%, p<0.0001). In multivariate analysis, germline mutation (RR=3.2; 95% CI 1.6-6.4, p=0.001), age, and symptoms were independent predictors of presence of IPMN, with no influence of family history of pancreatic cancer (p=0.22). Interestingly, the prevalence of IPMN was not distributed equally between all mutation types, ranging from 67% in patients with Peutz-Jeghers to 43% in HNPCC patients, 24% in BRCA2 patients, 14% in patients with ATM mutation, and 0% in CDKN2A, PALB2 or FAMM/p16 mutation patients.

Conclusion: In this series, 18% of mutation carriers harbored IPMN. A strong family history of PDAC was not an independent risk factor for developing IPMN. The prevalence of IPMN was highly variable depending on the mutation subtype. This series suggests that not all mutation carriers may develop precancerous lesions, and relying on cross-sectional imaging alone for screening and follow-up may be suboptimal. Genetic testing for patients with positive family history may help better tailor surveillance modalities for this high-risk population.
Background: Pancreatic Adenocarcinoma (PDAC) is the third leading cause of cancer related mortality, with an all stage 5 year prognosis of just 8%. Thus new systemic therapies are desperately needed. Semaphorin 4D (Sema4D) is a soluble and membrane bound glycoprotein which binds its cognate Plexin B1/B2 receptors, expressed on monocytes. Sema4D has been implicated in conferring a worse prognosis in some solid tumors, however, the prevalence and effect of Sema4D signaling in the context of PDAC remains largely undescribed. Here we present our findings in interrogating this axis, and build the preclinical rationale for a phase 1b/2 trial for combining FOLFIRINOX, Nivolumab and anti-Sema4D mAb (Pepinemab).

Methods: C57b/6 mice were orthotopically injected with murine PDAC line (KP2) derived from KRASG12D; TP53Flox/Wt; P48-Cre autochthonous tumors and confirmed for disease by high frequency ultrasound. Mice were treated with FOLFIRINOX (5-FU, Irinotecan, Oxaliplatin, weekly), immune checkpoint blockade (ICB) (anti-PD1, anti-CTLA-4 mAbs bi-weekly), and anti-Sema4D mAB (bi-weekly). Peripheral blood and tumor infiltrating leukocytes from patients with PDAC undergoing pancreaticoduodenectomy were assessed for Sema4D and Plexin B1/B2 via flow cytometry. Murine KP2 tumors were digested into single cell suspensions and stained for multiparameter flow cytometry for changes in immune subsets following treatment with anti-SEMA4D mAB. Human archival paraffin embedded tissues were sectioned and stained for immunohistochemical (IHC) targets for stromal components, immune subsets, and Sema4D.

Results: Flow cytometry of human PDAC demonstrates penetration of Plexin B1 positive leukocytes, most notably CD14+, CD68+ tumor associated macrophages. Quantitative IHC of resected PDAC tumors shows a significant penetration of Sema4D+ leukocytes compared to non-malignant pancreata (p<0.001) (Figure 1.A). Mice orthotopically injected with KP2 cells developed PDAC tumors detectable via high frequency ultrasound, and exhibited longer survival when treated with the combination of FOLFIRINOX, ICB, and anti-Sema4D antibody, compared to FOLFIRINOX alone, FOLFIRINOX and ICB, or FOLFIRINOX and anti-Sema4D antibody (P<0.001) (Figure 1.B). Flow cytometric analysis of combination anti-Sema4D and ICB treated murine tumors demonstrate a doubling of penetration by CD 8+ effector T cells within tumors (P=0.03) (Figure 1.C). Tumors from mice treated with anti-Sema4D mab, demonstrate a loss in Sema4D fluorescence signal on infiltrating CD3+ leukocytes (Figure 1.D), confirming target blockade within the tumor microenvironment.

Conclusion: Plexin B1+ myeloid subsets penetrate human PDAC tumors, and treatment with Sema4D blocking antibody improved response to ICB in combination with standard of care FOLFIRINOX in preclinical murine studies. Based on these findings, a Phase 1b/2 clinical trial in previously untreated unresectable PDAC was submitted and accepted on a competitive basis to the AACR/ASCO Methods in Clinical Cancer Research. The completed protocol is under institutional review and is expected to open in 2020 to test the safety, tolerability, and efficacy of combination Nivolumab, Pepinemab, and FOLFIRINOX.
21. SIGNIFICANCE OF "DOMINANT" UNCINATE DUCT DILATATION IN IPMN: A NEW HIGH-RISK CRITERION

Presenter: Samer AlMasri MD | University of Pittsburgh Medical Center

Background: The uncinate process of the pancreas has a dominant drainage ductal system that can either empty into the accessory or main pancreatic ducts. Although several autopsy series have outlined the anatomical footprints for this independent drainage system, current international consensus guidelines of intraductal papillary mucinous neoplasms (IPMNs) still consider it as a branch duct, even though it is the main drainage system for a once independent portion of the pancreas. We hypothesized that, in addition to the well-defined high-risk criteria of IPMNs, dilation of the “dominant” uncinate duct (UDD) is associated with advanced neoplasia (high grade dysplasia /invasive cancer = HGD/IC) on final resection pathology, and may therefore be classified as an independent high-risk criterion.

Methods: A retrospective review of patients who underwent surgical resection of a pancreatic IPMN between 2008-2019 at our institution was performed. Preoperative imaging studies (pancreas protocol CT and /or MRI) were reviewed by an abdominal radiologist who was blinded to the final pathological results. In addition to the Fukuoka criteria, we recorded whether there was any UDD irrespective of the location of the primary lesion. Using multivariate logistic regression, the pathological significance of UDD was determined.

Results: A total of 260 patients were identified. The mean age at diagnosis was 67.9 years and 49.2% were females. Of the entire cohort, 122 (47%) had HGD/IC and 138 (53%) had non-invasive (low/intermediate grade dysplasia) disease in the surgical specimen. UDD was noted in 59 (22.7%) patients, of which 36 (61%) had invasive disease on pathological evaluation (P < 0.003). On multivariate logistic regression for the entire cohort, adjusting for size, main duct dilation, presence of enhancing mural nodule, bilirubin level and demographics, UDD was an independent predictor of invasive disease (OR= 2.99, P < 0.04). Subgroup analysis was performed on patients with main/mixed duct IPMNs and branch duct IPMNs with high risk criteria confined to the dorsal pancreas (n=170, 66.4%) in order to determine the pathological significance of UDD in these remote lesions. Even in this subgroup of patients, UDD was a significant predictor of HGD/invasive cancer (OR= 7.6, P < 0.004), suggesting it may be associated with an aggressive field effect.

Conclusion: This is the largest study to date evaluating the significance of uncinate “dominant” duct dilation in IPMNs, and shows it to be a high-risk feature associated with HGD/IC. This association persisted for IPMNs limited to the dorsal pancreas, suggesting UDD may be associated with an aggressive “field effect”. Although these findings warrant validation with larger prospective studies, we recommend this feature be considered an additional high-risk criterion in IPMN, irrespective of the location of the cystic lesion.
Background: In the absence of any definitive therapy for delayed gastric emptying (DGE), effort should be focused to prevent it.

Methods: Patients were randomly allocated to end to side anastomosis (ES) and side to side anastomosis (SS) arms. Standard antrum preserving pyloric ring excision pancreaticoduodenectomy was carried out. Single loop reconstruction was performed with pancreatic, biliary and ante-colic gastric anastomosis in that order. End to side anastomosis was done by hand sewn technique using the entire length of the divided gastric margin, side to side anastomosis was done using staplers along the posterior gastric wall close to the greater curvature of stomach

Results: Of the 111 patients randomized, 40 were eligible in the end to side anastomosis (ES) and 43 in the side to side anastomosis (SS) arms. Both the groups were comparable in terms of demographic and clinical profile. The incidence of diabetes mellitus was similar in both the groups. Mean pancreatic duct diameter, pancreatic texture, operative time and blood loss was similar between the groups. Overall DGE was observed in 23 (28%) – grade A in 4%, grade B in 19%, grade C in 5%. SS group had significantly lower incidence of DGE (42% vs 12.5%, p=0.003). Clinically relevant DGE was lower in SS group (10% vs 37%, p=0.004). Primary DGE was lower in SS group (3% vs 23%, p=0.005), however, secondary DGE was comparable between the groups (10% vs 19%, p=0.27) On multivariate analysis, prolonged operative time (p=0.046, OR=2.02), end to side anastomosis (p=0.03, OR=9.36 ) and presence of pancreatic fistula (p=0.028, OR=9.11) were the predictors of DGE. SS group had early removal of nasogastric tube (6.1 vs 3.1 days, p=0.017), early resumption of solid diet (8.8 vs 5.1 days, p=0.006). SS group had a trend towards early discharge from the hospital (17.6 vs 14.0 days, p=0.13).

Conclusion: Construction of side to side gastro-jejunostomy resulted in reduced incidence of DGE with early removal of nasogastric tube, early resumption of oral solids and a trend towards early discharge from the hospital
23. NEOADJUVANT TREATMENT MITIGATES THE SURVIVAL IMPACT OF MAJOR COMPLICATIONS AFTER RESECTION OF PANCREATIC ADENOCARCINOMA

TE Newhook, JF Griffin, L Prakash, M Bruno, WL Dewhurst, N Ikoma, MP Kim, JN Vauthey, JE Lee, MHG Katz, CD Tzeng

Presenter: Timothy Newhook MD | The University of Texas MD Anderson Cancer Center

Background: While multimodality therapy is the current standard for resected pancreatic adenocarcinoma (PDAC), postoperative major complications (PMCs) may cause delay or omission of adjuvant therapy (AT) in patients undergoing surgery-first (SF) sequencing. Preoperative, or neoadjuvant, therapy (NT) may mitigate the impact of PMCs by ensuring delivery of multimodality therapy and reducing tumor burden before resection. We sought to evaluate the impact of PMCs on oncologic outcomes in patients treated with NT vs. SF in a contemporary cohort of PDAC patients treated with modern chemotherapy regimens.

Methods: Clinicopathologic data for consecutive PDAC patients who underwent pancreatectomy from July 2011-October 2018, were abstracted from a prospective database. PMCs were defined at 90 days as ACCORDION Grade ≥3. Overall survival (OS) durations were compared between patients with and without PMCs.

Results: Of 373 total patients, the majority underwent NT (75%). Most SF patients presented with potentially resectable disease (99%), whereas NT patients presented with potentially resectable (60%), borderline resectable (32%), and locally advanced (8%) classification (p<0.001). Of patients who received chemotherapy during NT, 47% received FOLFIRINOX, 51% a gemcitabine-based, and 2% other regimen. Median follow-up among survivors was 45 months (range 2-101 months). A PMC occurred in 22% of SF and 20% of NT patients (p=0.71). The majority of patients in both arms went on to receive some form of AT (90% SF vs. 70% NT, p<0.001). Despite nearly all SF patients receiving AT, the median OS was improved for patients who underwent NT sequencing as compared to SF (46 vs. 36 months, p=0.037). PMCs negatively impacted OS, with median OS of 59 months for NT without PMC, 34 months for NT with PMC, 45 months for SF without PMC, and 20 months for SF with PMC (p<0.001; Fig. 1A). OS was similar for patients who underwent SF without a PMC compared to NT with or without a PMC (p=0.13; Fig. 1A). On univariate analysis, there was a trend toward worse OS in NT patients who had PMCs (p=0.06, Figure 1B). On multivariable analysis of NT patients, while nodal positivity (HR-2.01, p=0.001) and pathologic major response (HR-0.37, p=0.035) were independent predictors of OS, PMCs were not. Among all patients, after adjustment for clinical classification, treatment sequencing, tumor size, and margin status, experiencing a PMC was an independent predictor of OS (HR-1.60, p=0.010), along with perineural invasion (HR-1.83, p=0.024), nodal positivity (HR-2.1, p<0.001), and AT receipt (HR-0.69, p=0.039).

Conclusion: The deleterious impact of PMCs on OS in patients with PDAC may be mitigated by NT sequencing. Given the significant risk of PMCs following pancreatectomy, as demonstrated in this and other studies, these results suggests that NT is the preferred treatment sequencing.
Figure 1: Overall survival of patients stratified by treatment sequence and incidence of PMC. NT, neoadjuvant therapy; PMC, postoperative major complication.
24. HIGH GRADE DYSPLASIA AND INVASIVE CARCINOMA AMONG SENDAI NEGATIVE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS
CL Wolfgang, N Amini, N Rezaee, GA Margonis, JL Cameron, RH Hruban, RA Burkhart, J He, M Makary, AM Lennon, MJ Weiss
Presenter: Neda Amini MD | Johns Hopkins University School of Medicine

Background: According to the current international guidelines, asymptomatic branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) without worrisome features, or high-risk stigmata – Sendai-negative IPMNs – should undergo conservative management with surveillance imaging studies. The aim of this study is to determine the risk of high-risk disease in Sendai-negative patients.

Methods: From February 1995 to January 2018, a total of 913 patients who underwent surgical resection for IPMN were identified. Sendai-negative patients were identified as those with no high-risk stigmata or worrisome features as defined by the international guidelines; namely, history of pancreatitis or jaundice, main pancreatic duct size ≥5 mm, cyst size ≥3 cm, presence of mural nodules or thickened cyst wall or septation, positive cyst fluid cytology for adenocarcinoma, and CA 19-9 ≥ 37 U/L. High-risk disease was defined as IPMNs with high-grade dysplasia or invasive carcinoma. Patients with concomitant pancreatic cancer, unknown pathology, or no preoperative imaging were excluded from the analysis.

Results: A total of 729 patients were included in this study. BD-IPMN was identified in 373 (51.2%), mixed-type in 265 (36.3%), and main-duct IPMN in 91 (12.5%) patients. Among 373 BD-IPMN, 99 (26.5%) were categorized as Sendai-negative. Compared to Sendai-positive patients, the Sendai negative group were younger (67 years vs. 70 years; P=0.039), mostly female (65.7% vs. 47.8%; P < 0.001), had higher rates of family history of pancreatic cancer (23.2% vs. 9.8%; P < 0.001), and lower rates of diabetes (14.3% vs. 32.2%; P=0.049). Among Sendai-negative patients, 12 (12.1%) had IPMN with high-grade dysplasia and only one patient (1.0%) had invasive carcinoma which was significantly lower compared to Sendai-positive patients (high-grade: 26.0%; invasive carcinoma: 28.7%; P < 0.001). Of note, age was the only factor associated with high-risk disease in Sendai-negative patients (median 66 years in low-risk vs. 72 years in high-risk IPMN; P=0.008). Interestingly, a family history of pancreatic cancer, smoking, and cyst size were not associated with high-risk disease in this group. The 5-year estimated overall survival was 84% in Sendai-negative patients with low-risk IPMN, which was comparable to 85.7% in Sendai-positive patients with high-risk IPMN (P=0.84; figure).

Conclusion: The risk of harboring a high-risk IPMN remains low in patients without worrisome features or high-risk stigmata. While close follow up is indicated in all patients with IPMN, higher risk of malignancy in elderly patients even in the absence of worrisome features or high-risk stigma should be considered. Of note, the incidence of high-risk IPMN might be overestimated among elderly patients due to a more selective operative approach.
V 1. COMPLEX LIVER RESECTION UNDER TOTAL VASCULAR EXCLUSION AND VENOUS RECONSTRUCTION WITH DOUBLE PERITONEAL PATCH
S Dokmak, B Aussilhou, F Cauchy, O Soubrane
Presenter: Safi Dokmak | Beaujon Hospital

Background: Patients necessitating complicated liver resection and venous resection-reconstruction of the vena cava or hepatic veins are traditionally operated under total vascular exclusion (TVE) and if prolonged (> 60 minutes), refrigeration and/or extracorporeal circulatory bypass can be needed. These procedures are associated with high morbidity and mortality. However with the advances in liver surgery techniques, resection can be simplified and performed during short duration TVE alone and venous reconstruction can be done with the peritoneum. We present the case of a patient who underwent 2 liver resections, both under vascular exclusion associated with venous reconstruction with the peritoneum.

Methods: For complicated cases and depending on the case, liver resection can be facilitated by the adoption of some surgical principles or techniques including (1) the thoracic incision for optimal exposition on the cavo-hepatic junction, (2) to do the maximum of dissection and liver transection with or without intermittent clamping of the hepatic pedicle and to preserve a short total vascular exclusion only for vascular reconstruction, (3) the use of the peritoneum for venous reconstruction, (4) the application of liver hanging maneuver, and (5) the experience of the surgeon.

Results: 47 year old female with colorectal liver metastases including with one with lateral invasion of the vena cava. Excellent response to chemotherapy and she underwent right hepatectomy extended to segment I, diaphragmatic resection with lateral resection reconstruction of the vena cava with a large peritoneal patch. Reconstruction was done under isolated clampage of the vena cava for 16 minutes. Surgery lasted 240 minutes with 500 ml of blood loss, transfusion of 2 units of blood. The postoperative course was uneventful. Two years later she present with recurrence invading the left hepatic vein with excellent response to chemotherapy. She underwent rehepatectomy with lateral reconstruction of the left hepatic vein with a peritoneal patch under isolated clampage of the hepatic pedicle for 25 minutes and total vascular exclusion for 20 minutes. Surgery lasted 240 minutes, with 200 ml of blood loss. The postoperative course was uneventful.

Conclusion: With improvements in surgical techniques, complicated liver resections can be done under short duration of TVE and venous reconstruction with the peritoneum.
V 2. LAPAROSCOPIC RIGHT HEPATECTOMY IN A CIRRHOTIC PATIENT: ANTERIOR APPROACH AND EXTRAFASSIAL PEDICLE CONTROL

JAP Kruger, GM Fonseca, VB Jeismann, FF Coelho, P Herman

Presenter: Jaime Kruger MD | Hospital das Clinicas - University of Sao Paulo

Background: Laparoscopic liver resections have gained progressive acceptance among liver surgeons. The second international consensus on minimally invasive liver operations indicated that major liver resections are increasingly being performed. Due to the complexity of such operations, most of them are performed in specialized tertiary academic centers. Along with the complexity of major resections, patient’s characteristics such as liver cirrhosis may increase procedure difficulty and demand different approaches in order to successfully perform the operation.

Methods: Video describing surgical technique for laparoscopic right hepatectomy. A 53 years-old male patient with hepatitis-C related cirrhosis was diagnosed with a right lobe hepatocellular carcinoma. The patient had normal liver function and no signs of portal hypertension. A totally laparoscopic right hepatectomy was performed, five ports were placed, a 10 mm 30 degree scope was used and pneumoperitoneal was set to 12 mmHg. Due to an enlarged an stiff liver an anterior approach was applied to avoid difficult mobilization and reduce hemodynamic stress. Pedicle was managed with an extrafascial extra hepatic approach and parenchymal transection was carried out with ultrasonic scalpel.

Results: Operative time was 360 minutes, estimated blood loss was 500 mL, no blood transfusion was required. Patient was discharged from ICU on 1st POD and from hospital on the 7th POD. The patient developed transient liver insufficiency (5th POD total bilirubin 2.05 mg/dL) and was discharged with improving clinical and biochemical tests. Pathology report confirmed a moderately differentiated HCC, 80 mm in the largest diameter associated with satellite nodules and microvascular invasion. The patient recurred 12 months after resection and was managed with TACE, being alive 30 months after operation.

Conclusion: Cirrhotic patients benefit from laparoscopic liver resection, which results in lesser blood loss and fewer liver-related complications. Anterior approach allows less liver mobilization with theoretical benefits of less hemodynamic stress and fewer microscopic tumor spillage into venous circulation. Exrafassial pedicle control is an interesting technical option for tumors located far from the pedicle as it results in complete control of the portal triad without prolonged hilar dissection.
V 3. ROBOTIC REVISION OF A POST-WHIPPLE HEPATICOJEJUNOSTOMY STRicture AFTER PREVIOUS OPEN PANCREATODUODENECTOMY

E Onkendi, Z Belal

Presenter: Zayne Belal | Texas Tech University Health Sciences Center

**Background:** Hepaticojejunostomy (HJ) is one of the three anastomoses made during a pancreatoduodenectomy (Whipple) procedure. A rare complication of a HJ anastomosis is a stricture, which is often symptomatic with pain, jaundice, cholangitis and potential biliary cirrhosis. The recommended initial treatment for this complication is to first attempt percutaneous dilations of the stricture and then perform surgical stricture revision if the percutaneous dilations fail. In this video, we describe a robotic approach to a post-Whipple resection hepaticojejunostomy stricture revision.

**Methods:** A robotic camera with 3 robotic arms and an assistant trocar were used for the procedure. The omental attachments to the free edge of the right liver were released until the hepatic hilum was exposed. The jejunal loop anastomosed to the bile duct was encountered and released from the surrounding attachments until the hepaticojejunostomy was fully identified and circumferentially dissected. The presumed bile duct portion of the HJ was grasped with robotic graspers to confirm the indwelling PTC tube and HJ. The HJ anastomosis was then opened over the PTC tube with electrosurgery until the tube was exposed. The tube was then retracted and the associated debris, stones and stricture were removed. The entire HJ was then taken down after the PTC tube was removed. The bile duct orifice was examined; it was thick-walled and measured roughly 7-8 mm in diameter. The HJ stricture scar was excised completely. The same jejunotomy was used for re-anastomosis. A new HJ was created with running posterior and anterior layers of 4-0 Vicryl sutures on RB-1 needles. The patency of the anastomosis was confirmed using a robotic grasper. The anterior and posterior sutures were then tightened and tied, completing the new HJ anastomosis. Surgical drain was placed around the HJ.

**Results:** The procedure time was 195 minutes with an estimated blood loss around 50 mL. The patient had an uneventful recovery postoperatively, and was discharged on post-operative day 2. The patient is currently doing well at 9 months postoperatively and will be followed up as needed.

**Conclusion:** Robotic hepaticojejunostomy stricture revision post-pancreatoduodenectomy feasible procedure. Previous open surgery should not contraindicate an attempt at minimally invasive repair if appropriate MIS/HPB skills and expertise is available. Robotic approach is had additional advantages in surgical dexterity due to increased range of motion/degrees of freedom, reduced surgeon fatigue and enhanced 3D visualization. Both access to a surgical robot and appropriately trained HPB surgeons are necessary to perform this procedure. This is often limited to large tertiary hepato-pancreato-biliary (HPB) surgery centers.
V 4. COMBINING ON-TABLE EMBOLIZATION WITH IMMEDIATE RESECTION TO SAFELY EXCISE GIANT HEPATIC HEMANGIOMAS

AV Maker, D Alrameni, N Prabhakar

Presenter: Ajay Maker MD | University of Illinois at Chicago

Background: The management of symptomatic giant hepatic hemangiomas varies in the literature. Multiple approaches have been described, and surgical resection is often used as a last resort due to the risk of major hemorrhage. One of the major difficulties in approaching massive hemangiomas is safe control of the substantial arterial inflow since the porta, feeding vessels, and outflow may be inaccessible to due to tumor size and immobility. Preoperative arterial embolization is an option, however, many patients will experience severe pain, fever, transaminitis, acidosis, recanalization, and collateral inflow that limit its utility. Furthermore, patients will require post-procedure inpatient observation that extends hospital costs and length of stay, and there is no consensus on the appropriate time interval between procedures. We endeavored to approach this clinical situation with on-table angiogram and embolization followed by immediate resection in a hybrid operating room.

Methods: Under general anesthesia in a hybrid operating room with on-table angiogram capabilities, the patient underwent a celiac and SMA angiogram followed by hemangioma inflow embolization and immediate hepatic resection.

Results: Two large branches of the left hepatic artery were feeding a >20cm hemangioma. The mass replaced the left hepatic lobe and displaced the middle hepatic vein. After coil embolization of the arterial inflow to the tumor, the femoral sheath was removed and the patient was immediately prepped and draped for hepatic resection on the same table. Tumor size was substantially reduced and the hemangioma was compressible, allowing mobilization of the tumor and access to the porta hepatis. Left hepatic arterial and portal inflow were ligated, outflow was controlled, and the parenchyma was divided combining formal resection planes with enucleation of the tumor off the middle hepatic vein at its origin. Blood loss was minimal (<150mL) and the patient was discharged home on no pain medicine and free of preoperative symptoms on post-operative day 4.

Conclusion: Combining on-table embolization with immediate resection avoids post-procedure pain and many of the pitfalls of preoperative embolization. It is an efficient use of hospital resources and reduces an intervening hospital admission. We have found it to be a preferred approach to enhance the safety and feasibility of resection for massive hepatic hemangiomas with minimal intraoperative blood loss and reduced risk.
V 5. TBD
Background: Caudate tumors are not uncommonly encountered. Resection is complicated because of the caudate lobe’s intimate relationship to the proper hepatic artery, porta hepatis, and inferior vena cava. Laparoscopic caudate lobectomy is infrequently performed because of the risk of hemorrhage and the high level of technical skill required to complete the operation safely in minimally-invasive fashion.

Methods: We describe a laparoscopic caudate lobectomy in a 63 year old gentleman with pancreatic neuroendocrine tumor metastatic to the caudate lobe. Pre-operative imaging demonstrates that the proper hepatic artery, left portal pedicle, and inferior vena cava are the critical nearby structures. The ligamentum venosum and main portal vein branch supplying the lobe are visible.

Results: The patient is positioned supine with split leg table. Standard laparoscopic cholecystectomy port locations were used. The gastrohepatic ligament was incised. The caudate lobe was grasped and retracted cephalad and anteriorly. Draining hepatic veins into the IVC were carefully ligated with a laparoscopic bipolar energy device. The lobe was then retracted toward the patient’s left and the ligamentum venosum was ligated. Parenchymal transection was completed with waterjet dissection. The main portal vein supply was ligated with clips. The caudate lobe was freed of remaining attachments and removed in a bag.

Conclusion: If care is taken, caudate lobectomy can be performed safely in minimally invasive fashion. Use of waterjet dissection can mitigate risk of injury to the IVC with ultrasonic dissection device. Meticulous surgical planning is required to ensure successful and safe completion.
V 7. MANAGING POTENTIALLY FATAL BLEEDING DURING LAPAROSCOPIC HEPATECTOMY: INTRACORPOREAL SUTURING

JAP Kruger, GM Fonseca, VB Jeismann, FF Coelho, P Herman

Presenter:  Jaime Kruger MD  | Hospital das Clinicas - University of Sao Paulo

Background: Laparoscopic liver surgery has evolved substantially along last years and has gained progressive acceptance among liver surgeons. Despite minimally invasive, hepatic resection remains a complex procedure associated with operative complications frequently related to blood loss. Operative hemorrhage is the most common cause to conversion during laparoscopic operations. In instances of massive bleeding conversion may not be the solution since it takes time to open the cavity, place retractors and finally manage the bleeding spot. Another risk during conversion for venous defects is air embolism with non diffusible gases.

Methods: Three cases of intraoperative hemorrhage are shown. The first case is a laparoscopic right hepatectomy and bleeding occurred during liver mobilization, when transecting the right coronary ligament an inadvertent lesion occurred to the wall of the right hepatic vein. In this case the surgeon was experienced in both open and laparoscopic liver surgery. Case two depicts a surgeon during the course of his learning curve on liver resection performing a left lateral sectionectomy in which during final phase of liver transection an inadvertent lesion is inflicted to the root of the left hepatic vein. Third case describes another planned right hepatectomy in which a hemostatic clip slips from the inferior vena cava, while dissection is carried out by an experienced conventional liver surgeon, but still climbing the learning curve for minimally invasive operations.

Results: All three cases were managed with intracorporeal suturing avoiding conversion. The first two cases did not require blood transfusion and the third patient received two units of packed red blood cells.

Conclusion: Potentially fatal hemorrhage can occur at any point of a surgeon’s learning curve and at any point of a liver operation. This video shows hemorrhagic events during mobilization, transection and vascular control. Liver surgeons dealing with laparoscopic resections must be trained in both advanced liver and laparoscopic surgery in order to manage operative complications in which the conversion may be riskier than laparoscopic management.
25. TRAVELING TO REACH HIGH-VOLUME CENTERS AMONG PATIENTS UNDERGOING HEPATECTOMY: HOW FAR WILL YOU GO?
A Diaz, A Ejaz, J Cloyd, A Manilchuk, M Dillhoff, J Bean, A Tsung, T Pawlik
Presenter: Adrian Diaz MD, MPH | The Ohio State University

Background: While better outcomes at high-volume surgical centers have driven regionalization of complex surgical care, access to high-volume centers often requires travel over longer distances. We sought to evaluate travel patterns among patients undergoing hepatectomy to assess willingness of patients to travel for surgical care.

Methods: The California Office of Statewide Health Planning database was used to identify patients who underwent hepatectomy between 2005-2016. Total distance traveled, as well as whether a patient bypassed the nearest hospital that performed hepatectomy to get to a higher-volume center was assessed. Multivariate analyses were used to identify factors associated with bypassing a local hospital for a higher-volume center.

Results: Overall 13,379 adults underwent a hepatectomy in 229 hospitals; only 39 hospitals were considered high volume (15+ cases/year). Median travel distance to a hospital that performed hepatectomy was 21 miles (IQR: 9.2-47.8) with a median travel time of 25 minutes (IQR: 13.1 – 52.0). The overwhelming majority of patients (92%) bypassed the nearest providing hospital to seek care at a destination hospital. Among patients who bypassed a closer hospital, 75% went to a high-volume hospital. Outcomes at hospitals with shorter travel distances versus destination hospitals varied (incidence of complications: 23% vs. 20%; failure-to-rescue: 11% vs. 7%; mortality 2.6% vs. 0.5%; all p&lt;0.05). Care at a high-volume center for hepatectomy was associated with hospital bypass (OR=4.23 95%CI 3.68–4.89). Of note, African American (OR=0.55 95%CI 0.46 – 0.66) and Hispanic (OR=0.66 95%CI 0.59 – 0.74) patients, as well as individuals with Medicaid (OR=0.55 95%CI 0.47 – 0.63), were less likely to undergo care at a high-volume center or travel more than 25 minutes for care (AA: OR=0.41, 95%CI 0.35- 0.49; Hispanic: OR=0.61, 95%CI 0.55-0.68; Medicaid: OR=0.72 95%CI 0.63-0.83)(all p&lt;0.05). Among the 3,703 patients who underwent hepatectomy at a low volume center, 2,126 (57.4%) patients had bypassed a high-volume hospital. Among the remaining 1,577 patients, 95% of these individuals would have needed to travel less than an additional hour to reach a high-volume center.

Conclusion: Roughly one-quarter of patients who underwent hepatectomy received care at a low-volume center, with African-American, Hispanic, and patients on Medicaid particularly at risk. Nearly all of these patients either bypassed a high-volume hospital or would have needed to travel less than one additional hour to reach a high-volume center.
- High Volume Hospital  ○ Bypassed HVH  ● < 60 minutes  ★ >60 minutes

NOTES: Empty circles represent patients who bypassed a high volume hospital on the way to their destination low volume hospital. Grey circles represent patients who would have needed to travel an additional 60 minutes or less from their destination hospital to nearest high volume hospital. Stars represent patients who would have needed to travel greater than 60 minutes from their destination hospital to nearest high volume hospital.
26. PREOPERATIVE APRI+ALBI SCORE ALLOWS RISK STRATIFICATION PRIOR TO LIVER RESECTION

P Starlinger, DS Ubl, RL Smoot, SP Cleary, EB Habermann

Presenter: Patrick Starlinger MD | Mayo Clinic, Rochester

Background: Preoperative risk assessment for postoperative liver dysfunction (LD) still poses a major challenge in patients undergoing liver resection. Currently, only limited options are available to easily assess liver function prior to surgery. Aspartate Aminotransferase/Platelet Ratio Index (APRI) and Albumin-Bilirubin Grade (ALBI) are validated markers in patients suffering from hepatic pathologies. Previously, both markers have been implicated as a valid predictor for postoperative LD after liver resection. We were recently able to demonstrate a highly significant and clinically relevant predictive value of the combination of the APRI and ALBI score to predict postoperative outcome after liver resection. Within this analysis, we aimed to validate our exploratory findings in a larger cohort and subsequently develop a web based application system to facilitate easy clinical translation.

Methods: Assessing the National Surgical Quality Improvement Program (NSQIP) database, we identified 13401 patients undergoing liver resection from 2014 to 2017 for preoperative blood values and detailed 30-day postoperative outcomes. Preoperative APRI+ALBI score was calculated from these routine laboratory tests. Association of APRI+ALBI with postoperative LD as well as morbidity and mortality was assessed via univariate analyses.

Results: The combination of both scores (APRI+ALBI) significantly differed between groups (LD: median -3.92; No LD: median -4.18, P=0.002) and was further found to be superior over each score alone. This association was particular significant if patients undergoing major liver resection. Further, APRI+ALBI gradually decreased with postoperative LD grade (No LD: median -4.03, grade A LD -3.96, grade B LD: -3.52, grade C LD: -3.47 (P < 0.001). In line with these results, higher preoperative APRI+ALBI levels were also observed in patients suffering from postoperative morbidity (P < 0.001), and mortality (P=0.001). Detailed results are illustrated in Table 1. We further developed a web based application to calculate the APRI+ALBI score to define the specific risk of postoperative LD morbidity and mortality of each individual score result.

Conclusion: We were able to validate our recent exploratory findings, confirming that the combination of APRI and ALBI is vital to predict postoperative outcome after liver resection with highest accuracy. Further we developed a web based application to allow clinical translation of these findings and facilitate quick and easy risk assessment prior to liver resection using routine laboratory parameters.
<table>
<thead>
<tr>
<th></th>
<th>APR + ALBI</th>
<th>APR - ALBI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All (n=13401)</strong></td>
<td><strong>No PHRF (n=12192)</strong></td>
<td><strong>Yes - PHRF (n=1209)</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td>No. (% used)</td>
<td>11665 (86.5%)</td>
<td>10000 (81.5%)</td>
<td>147 (90.4%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-4.61 (2.47)</td>
<td>-4.09 (2.52)</td>
<td>-0.91 (0.82)</td>
</tr>
<tr>
<td>Range</td>
<td>505.335-10000</td>
<td>500.955-10000</td>
<td>5.3733-1259.24</td>
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**All (n=13401)** | **No Major Complication within 30 Days of Procedure (n=11974)** | **Any Major Complication within 30 Days of Procedure (n=2027)** | **P-value** |
| No. (% used)     | 11665 (86.5%) | 9965 (82.2%) | 1709 (89.8%) |
| Mean (SD)        | -4.61 (2.47)  | -4.03 (2.39) | -0.73 (0.82) |
| Range            | 505.335-10000 | 500.955-10000 | 5.3733-1259.24 |

**All (n=13401)** | **No Mortality within 30 Days of Procedure (n=12192)** | **Death within 30 Days of Procedure (n=1209)** | **P-value** |
| No. (% used)     | 11665 (86.5%) | 11277 (85.5%) | 178 (81.3%) |
| Mean (SD)        | -4.61 (2.47)  | -4.02 (2.46) | -0.72 (1.12) |
| Range            | 505.335-10000 | 500.955-10000 | 5.3733-1259.24 |
Background: Frailty is highly prevalent in patients with malignancy and is associated with high risk of morbidity and mortality after operative interventions. However, the impact of frailty on patients undergoing liver resection for metastatic colorectal cancer has not been studied. The aim of this study was to assess the impact of frailty on short term outcomes after liver resection in patients with metastatic colorectal cancer to the liver.

Methods: We performed a 4 year analysis of the National Surgical Quality Improvement Program (NSQIP) participant user files. All patients undergoing hepatectomy for metastatic colorectal cancer between 2014-2017 were reviewed. The 5-item Modified Frailty Index (mFI) was calculated using NSQIP variables. We included all patients with complete mFI information in the analysis. Patients were divided into three categories based on the mFI (0= no frailty indicators, 1=one frailty indicator, 2=two or more frailty indicator). Outcome measures in house included minor and major morbidity as defined by the Clavien-Dindo classification (I/II vs III/IV), 30 day mortality, need for readmission, unfavorable discharge (not to home), bile leak and liver failure.

Results: A total of 5230 patients were included in the analysis. 2737 (52%) had a mFI score of 0, 1839 (35%) had a mFI score of 1, and 654 (13%) had a mFI score of 2 or more. On multivariate analysis and after adjusting for potential confounders such as age, sex, race/ethnicity, BMI, ASA class, preoperative albumin, neoadjuvant chemotherapy and extent of surgery (minor vs major); patients with a mFI score of 2 or over were more likely than those with mFI of 0 to experience minor morbidity (OR 1.47, 95% CI 1.14-1.91, p<0.01), major morbidity (OR 1.82, 95% CI 1.29-2.55, p<0.01), readmission (OR 1.56 95% CI 1.10-2.23, p<0.01), non-home discharge (OR 2.81, 95% CI 1.74-4.50, p<0.01), and bile leak (OR 1.64 95% CI 1.05-2.54, p=0.03). Those with a mFI score of 1 were more likely than those with mFI 0 to experience non-home discharge (OR 1.54 95% CI 1.03-2.31 p=0.04) and liver failure (OR 1.63, 95% CI 1.14-2.45, p<0.01).

Conclusion: Frailty is associated with increased risk of morbidity, unfavorable discharge, readmission and bile leak in patients undergoing liver resection for metastatic colorectal cancer. We recommend the use of the 5-item Modified Frailty Index to guide risk stratification, optimization and counseling.
CD47 BLOCKADE INHIBITS HEPATOCELLULAR CARCINOMA PROGRESSION BY DISRUPTING ALTERNATIVELY ACTIVATED TUMOR-ASSOCIATED MACROPHAGES

F Zhou, M Xu, B Rabe, DL Chirumbole, X Wang, GA Upadhya, Y Lin, WC Chapman

Presenter: Fangyu Zhou | Washington University, St. Louis

Background: Immunotherapy has great potential for the treatment of hepatocellular carcinoma. One area of active investigation involves the CD47 signaling pathway, which is used by normal tissues as a “don’t eat me” self-signal to inhibit macrophage phagocytic activity. Various cancers, including HCC, have been found to over-express CD47 to evade macrophage tumor surveillance. In an animal model, we found previously that CD47 signaling blockade with monoclonal antibodies (CD47mAb) can overcome this evasion mechanism and results in tumor shrinkage. Although this anti-tumor activity is thought to pivot on blocking SIRPα binding on macrophages to CD47 of tumor cells, the full extent of the immune response is not well-understood. Reports have demonstrated that alternatively activated macrophage (M2) is predominantly present in tumor microenvironment, facilitating immune evasion through interaction with tumor cells. We hypothesized that CD47 blockade results in the disruption of tumor associated macrophage population, which then leads to recruitment of tumor-suppressive macrophages and thus effect the anti-tumor activity of the signaling blockade.

Methods: MHCC-97L tumor cells were implanted into NOD scid gamma (NSG) mice, which have functional macrophages and neutrophils and absent B-cells, T-cells and NK cells. After which they were given 4 weeks of CD47 blockade treatment via intra-peritoneal injections of CD47mAb or isotype IgG as control. The animals were euthanized after treatment. Tumors were explanted and assayed for macrophage infiltration and polarity via immunofluorescence.

Results: A) Tumor growths between control group (Isotype IgG, n=4) and treatment group (CD47mAb, n=4) are significantly different starting day 15 to end of treatment at day 31 (****p<0.001). B) Mice received CD47 blockade treatment display significantly lighter tumor burden comparing to control group (Day 31, 0.64±0.29g vs. 2.28±0.78g, **p=0.008). C) Immunofluorescence staining in explanted tumors after CD47mAb treatment shows decreased CD206+ cells and increased F4/80+ cells infiltration in tumor mass comparing to isotype IgG control. Focal loss of DAPI signals are observed in CD47mAb treatment group, suggesting tumor destruction after CD47 blockade.

Conclusion: Our results suggest that CD47 blockade via CD47 monoclonal antibody results in tumor-associated macrophage pivoting from tumor-protective alternatively activated state(M2) to tumor-suppressive classically activated state(M1), leading to inhibition of hepatocellular carcinoma progression in tumor-bearing mice. Further investigation in mechanisms and interactions with other cell types are warranted.
29. PRE-SURGERY NEUTROPHIL EXTRACELLULAR TRAP LEVELS PREDICT RECURRENCE-FREE AND OVERALL SURVIVAL FOR HEPATIC MALIGNANCIES
S Tohme, C Kaltenmeier, H Yazdani, D Geller, A Tsung
Presenter: Christof Kaltenmeier MD | University of Pittsburgh Medical Center

**Background:** A systemic inflammatory state is widely considered as a preoperative risk factor for outcomes in solid organ malignancies. Neutrophils have been known to play an important role during early and chronic inflammation. Neutrophil to lymphocyte ratio (NLR) is a well-recognized sensitive measure of inflammation and high NLR levels have been linked to risk of cancer recurrence. After activation, neutrophils release their DNA into the extracellular space, referred to as neutrophil extracellular traps (NETs). This is a defense mechanism first described to trap and kill bacteria and other pathogens, however has recently been identified in the pathogenesis of inflammatory and malignant diseases. We have recently shown that neutrophil extracellular traps (NETs) play a critical role and can promote the development and progression of liver metastases after surgical stress in mice. The current study uses a specific neutrophil marker – neutrophil myeloperoxidase (MPO-DNA) as a measure of NET formation. MPO is released into the extracellular space during neutrophil degranulation. We hypothesize that NETs can be utilized as a biomarker determining outcomes after resection of hepatic malignancies.

**Methods:** We selected 103 consecutive patients with Hepatocellular carcinoma (HCC) or Cholangiocarcinoma (CC) who underwent surgery at our institution. Preoperative serum levels were routinely collected for tissue banking. Neutrophil number and MPO-DNA levels were measured pre-surgery. We then performed log rank analysis of recurrence-free survival in patients with high vs low MPO-DNA/NLR. In addition, Pearson correlation of pre-operative MPO-DNA and NLR was performed.

**Results:** Pre-therapy MPO-DNA levels are strongly associated with recurrence-free survival in patients undergoing surgery for HCC or CC. Patients with higher pre-therapy MPO-DNA were more likely to have a shorter disease-free survival compared to those with low levels. (HCC: HR: 2.909, 95% CI: 1.607 to 5.264, p<0.0001, CC: HR: 3.221, 95% CI: 1.335 to 7.773 p<0.0093). Median survival for HCC patients with high vs low MPO-DNA was significant with 12.6 vs 25.8 months. Similar results were obtained in CC patient, high vs low MPO DNA was significant with 13.6 vs 42.9 months. In addition, there is a significant correlation between pre-therapy NLR and MPO-DNA for both HCC and CC (HCC: p<0.0001, R2 = 0.22, CC: p<0.0065, R2 = 0.28) (Figure 1).

**Conclusion:** Neutrophils are an important marker for hepatic cancers after resection. The current study focuses on pre-therapy levels of MPO-DNA as a prognostic marker of recurrence free survival following surgery. This study showed that high pre-therapy NET levels are indicative of poor outcomes in patients undergoing surgery for HCC and CC.
Background: Racial/ethnic and socioeconomic disparities are assumed to negatively affect treatment and outcomes for hepatocellular carcinoma (HCC). Our aim was to investigate the interaction of racial/ethnic and socioeconomic factors with stage of disease and type of treatment facility in receipt of treatment and overall survival (OS) of patients with HCC.

Methods: We included all patients with primary HCC in the US Safety-Net Collaborative database (2012-2014), which is comprised of five highly select, geographically diverse safety-net hospitals (SNH) and their corresponding quaternary-referral center. Patients were categorized into “safety-net” or “academic” based on where they received treatment. Socioeconomic factors were determined at the zip-code level and included median income, and percent of adults who graduated from high-school. Primary outcomes were receipt of treatment and OS.

Results: 1832 pts were included. Average age was 61yrs and 77%(n=1405) were male. 57%(n=1039) were treated at academic and 43%(n=793) at safety-net hospitals. Patients treated at SNH were younger (59vs63yrs), less likely to be white (40vs65%), and more likely to be uninsured (27vs4%), have lower median income ($43,001vs$52,598), and live in areas in which fewer adults graduated from high school (84vs76%)(all p<0.001). SNH patients were more likely to have a history of alcohol abuse (51vs40%) and to present with stage IV disease (25vs14%); they were less likely to have been previously radiographically screened (17vs27%) or to receive treatment (65vs83%)(all p<0.001). SNH patients had decreased 5-year OS compared to their academic counterparts (24vs37%, p<0.001).

On MV Cox regression, neither race/ethnicity, median income, nor care provided at a SNH were directly associated with decreased OS (all p>0.05). Independent predictors of decreased OS included having no insurance (HR 1.34), less educational attainment (HR 1.59) higher MELD score (HR 1.07), higher stage at diagnosis (II: HR 1.34, III: HR 2.87, IV: HR 3.23), and not receiving treatment (HR 3.94)(all p<0.05).

Factors associated with not receiving treatment on MV analysis included history of alcohol abuse (HR 0.682), increasing MELD (HR 0.874), and higher stage at diagnosis (III: HR 0.234, IV: HR 0.210). Although these characteristics were more common in patients treated at SNH, race/ethnicity, socioeconomic status as measured by income and education, and treatment at a SNH were not associated with receipt of treatment. Of patients who actually received treatment, there were no racial/ethnic or socioeconomic disparities in survival. Instead, survival was dictated by MELD, treatment modality, and stage at presentation. Patients who were screened were more likely to present with stage I disease (62vs39%) and to receive treatment (86vs72%, all p<0.001), both important factors associated with improved survival.

Conclusion: The interplay of race/ethnicity, socioeconomic factors, disease biology, and the condition of the host liver is complex as it relates to treatment and outcomes of patients with HCC. While there is overlap amongst all these factors, there is no intrinsic or direct association of race/ethnicity, socioeconomic status, or being treated at select safety-net hospitals with worse outcomes. Poor liver function, no insurance, and advanced stage of presentation are the main determinants of not receiving treatment and decreased survival. Efforts directed towards education, government aid, and screening programs for vulnerable and at-risk patients who receive their care at safety-net hospitals are needed.
31. CIRRHOSIS-DRIVE IMMUNE DYSFUNCTION ASSOCIATES WITH POOR RESPONSE TO DEB-TACE AND WAITLIST DROPOUT IN HEPATOCELLULAR CARCINOMA PATIENTS

K Nunez, T Sandow, M Hibino, A Cohen, P Thevenot

Presenter: Kelley Nunez PhD | Ochsner Health System

**Background:** Hepatocellular carcinoma (HCC) recurrence after transplantation is associated with higher tumor grade on explant, failure to respond to DEB-TACE, and pretreatment lymphopenia. We prospectively monitored HCC patients in transplant evaluation to investigate associations between lymphopenia and tolerance with treatment response and waitlist outcomes.

**Methods:** HCC patients undergoing DEB-TACE were prospectively enrolled. Blood was collected before and after DEB-TACE (100-300µm LC Beads with 100mg doxorubicin). Peripheral blood mononuclear cells were analyzed by flow cytometry. Tumor response to DEB-TACE was determined using mRECIST imaging criteria. Intention-to-treat (ITT) endpoint included transplantation or tumor progression.

**Results:** Analyzed were 91 patients with a median age 61, predominantly Caucasian (73%) with Hepatitis C (80%). Prior to DEB-TACE, 47% of patients were lymphopenic (absolute lymphocyte count, ALC≤1.2k/μL). Tumor response was scored using mRECIST and available in 82 patients. Pre-treatment ALC and lymphopenia status were associated with failure to respond to DEB-TACE (P=0.028, P=0.004). Overall, 69% of patients that did not respond to treatment were lymphopenic. These patients also exhibited significantly lower albumin (P=0.0017) and higher bilirubin (P=0.02) at the time of treatment. Interestingly, no significant changes were observed in lymphocyte count, albumin, and bilirubin levels between 3 years prior to HCC development, at the time of diagnosis, and day of treatment. Tolerogenic immune populations, myeloid derived suppressor cells (MDSC) and regulatory T cells were significantly elevated in lymphopenic patients (P=0.02 and P=0.001). MDSCs isolated from HCC patients exhibited immune suppressive activity. To investigate whether bilirubin could impact T cells, isolated human T cells were incubated with unconjugated bilirubin; results showed no effect on proliferation. Sixty patients (66%) reached ITT endpoint with 30/60 transplanted and 30/60 waitlist dropout due to tumor progression. In the ITT cohort, 61% of patients that did not respond to treatment experienced tumor progression.

**Conclusion:** Lymphopenic status remains stable prior to HCC development and may be cirrhosis-driven. Patients presenting with lymphopenia and poor liver synthetic function can identify patients with immune dysfunction both at risk of tumor progression prior to transplantation.
32. IS MANDATORY ROUTINE CAUDATE LOBE RESECTION INDICATED IN HILAR CHOLANGIOCARCINOMA?

L Yohanathan, TS Yamashita, K Croome, SP Cleary, TE Grotz, ML Kendrick, MJ Truty, RL Smoot, DM Nagorney

Presenter: Lavanya Yohanathan MD | Mayo Clinic, Rochester

Background: Necessity for routine resection of caudate lobe as part of liver resection in hilar cholangiocarcinoma (CCA) is controversial. The caudate lobe is an anatomic component of resectability where careful preoperative planning with assessment of imaging should factor into whether resection is indicated. We sought to evaluate if hepatectomy with caudate resection compared to those without caudate resection affected overall survival.

Methods: We reviewed data for all patients undergoing hilar cholangiocarcinoma (HCCA) resection between 1993-2017. Operative notes were reviewed to evaluate whether caudate lobe resection was undertaken. Extent of liver resection was recorded. Frozen section and final pathology status for was reviewed. Overall survival was the primary outcome. Progression free survival and recurrence pattern were secondary outcomes.

Results: 178 patients underwent hepatic and bile duct resection with regional lymphadenectomy and Roux Y hepaticojejunostomy for HCCA. Of 178 patients, 100 (56%) patients underwent caudate resection (CR) whereas 78 (44%) patients did not have their caudate lobes (NCR) resected. There was no significant difference in patient demographics or tumor characteristics. 88% of patients underwent a preoperative biopsy and the mean CA 19-9 level amongst both groups was 26.5 (17.7-38.2). Majority of these tumors were poorly differentiated (NCR:50%, CR:42.4%) followed by moderately differentiated (NCR, CR: 42.4%). Of 178 pts, 87 pts (48.9%) had a left hepatectomy, of which 81 pts had caudate lobe resection. 84 pts (47.2%) underwent a right hepatectomy .4 pts (2.2%) had a right trisegmentectomy, of which 17 and 2 patients had their caudate lobe resected respectively. Liver margins were negative in 95% of pts in NCR group and 97% in the CR group (p=0.36). Lymph node metastases were present in 43% of pts in the NCR group and 32% in CR group (p=0.14). There was no significant difference in postoperative mortality (p=0.78). Higher rates of postoperative bile leak occurred in the NCR group 37.7% versus the CR group 21% (p=0.02) necessitating higher rates of percutaneous drain placement in the NCR group (36% vs.18%, p=0.005). Biliary fistula occurred in 17.6% of patients in NCR group compared to 7.2% in the CR group (p=0.11). Median overall survival was 28.4 and 44 months in the NCR and CR groups respectively (p=0.28). A higher proportion of patients in the NCR group received adjuvant chemotherapy (40%) and postoperative radiation (21%) when compared to CR group where 34% of pts received adjuvant chemotherapy and 13% postoperative radiation. Most frequent recurrence was within the liver and hepaticojejunostomy site. Peritoneal and extrahepatic recurrences were fewer. Intrahepatic recurrence occurred in 6/22(27%) in the NCR group and 18/355 (51%) in CR group (p=0.13). Median progression free survival was 19.8 and 33.7 months in the NCR and CR groups (p=0.34).

Conclusion: Routine caudate lobe resection does not confer survival advantage in patients undergoing liver resection, regional lymphadenectomy and Roux Y reconstruction for hilar cholangiocarcinoma. Nodal status had no impact on survival related to CLR. The decision to resect caudate lobe should be based on radiological imaging, tumor characteristics, and pathologic evaluation with the ultimate goal of achieving a R0 resection.
Background: As minimally invasive approaches (MIS) to biliary tract cancers become more commonplace, understanding whether they offer adequate locoregional clearance is critical. We sought to study how laparoscopic and robotic surgery compare to open surgery for the various surgical quality measures for intrahepatic cholangiocarcinoma (ICC) and gallbladder cancer (GBC).

Methods: The National Cancer Database was queried for all patients who underwent hepatic resection of ICC of any stage and T1b or more advanced GBC between 2010 and 2016. Patients were grouped by surgical approach: open (OA), laparoscopic (LA), and robotic (RA). To measure appropriateness of oncologic therapy between open and MIS approaches, rate of lymph node dissection, quality of lymph node dissection, and R0 resection rate were evaluated. In addition, length of stay and 30 day-readmission were assessed. Statistical analyses were performed using SAS EG7.1 (Cary, NC). Statistical significance was defined as p<0.05.

Results: In this cohort of 8,612 patients, an MIS approach to resection was used 40% of the time. Hepatic resection was performed for 4,034 patients with ICC (OA: 3,281, LA: 675, RA: 78) and radical cholecystectomy for 4,578 with GBC (OA: 1,893, LA: 2,588, RA: 97). MIS is being used with increasing frequency (ICC [2010 to 2016]: 14% to 20% and GBC [2010 to 2016]: 48% to 66%, p<0.001). For the entire study cohort, R0 resection was achieved in 71% OA, 67% LA, and 77% RA, p<0.001. Rates of lymph node dissection were 58% for ICC (OA: 61% LA: 46% RA: 44%, p<0.001) and 49% for GBC (OA: 59% LA: 41% RA: 58%, p<0.001). When lymphadenectomy was performed, the mean number of lymph nodes examined was 4.4 (OA: 4.7 LA: 3.7 RA: 4.9, p<0.001). Among ICC patients who underwent lymphadenectomy, examination of 6+ lymph nodes was achieved more commonly with a robotic approach (OA: 27%, LA 24%, and RA: 35%, p<0.001). Median length of stay was longest with an open approach [ICC [OA: 7, LA: 6, RA: 5] and GBC [OA: 5, LA: 3, RA: 3]], days, p<0.001). Unplanned 30-day readmission rates were similar between open and MIS approaches (OA: 7% vs. MIS: 6%, p=0.274).

Conclusion: As the application of laparoscopic and robotic surgery in the treatment of GBC and ICC continues to increase, monitoring their surgical quality will be paramount. Laparoscopy, in particular, may fall short in achieving quality metrics of margin-negative resection and adequate regional lymphadenectomy.
34. THE TYROSINE PHOSPHATASE SHP2 REGULATES YAPY357 PHOSPHORYLATION, AND IN VIVO SENSITIVITY TO CYTOTOXIC CHEMOTHERAPY IN CHOLANGIOCARCINOMA

E Buckarma, N Werneburg, A Niibe, G Gores, R Smoot
Presenter: EeeLN Buckarma MD | Mayo Clinic, Rochester

Background: Cancer of the biliary tract, cholangiocarcinoma (CCA), is increasing in incidence and has limited treatment options. In an attempt to further understand signaling pathways driving oncogenesis and impacting response to therapy we, and others, have identified altered activation of the transcriptional co-activator, Yes-associated protein (YAP) in CCA. Canonical regulatory pathways impacting YAP consist of serine kinases; however, more recently we have demonstrated a central role for tyrosine phosphorylation in regulating YAP function in CCA. Herein we explore the role of tyrosine phosphatases in regulating YAP tyrosine phosphorylation and sensitivity to current cytotoxic chemotherapy.

Methods: Molecular studies utilized the human CCA cell lines HuCCT-1 and KMCH. Baseline tyrosine phosphatase levels were assessed by RT-PCR and immunoblot. YAP-interacting phosphatases were identified by co-immunoprecipitation. The selective tyrosine phosphatase inhibitors NSC87877 and SHP099 were utilized. Tyrosine phosphorylation was assessed by immunoblot. YAP transcriptional activity was evaluated by RT-PCR for YAP target genes. SHP2 levels were modulated utilizing knockout via a doxycycline-inducible CRISPR/Cas9 system. Enforced expression of SHP2 was explored utilizing catalytically active and dead constructs. Tyrosine phosphorylation was assessed by immunoblot. YAP transcriptional activity was evaluated by RT-PCR for YAP target genes. SHP2 levels were modulated utilizing knockout via a doxycycline-inducible CRISPR/Cas9 system. Enforced expression of SHP2 was explored utilizing catalytically active and dead constructs. YAP subcellular localization was assessed by immunofluorescence. Proliferation was evaluated by MTS assay and cell viability was assessed with Cell Titer-Glo. Cytotoxic agents' gemcitabine and cisplatin were utilized for in vitro and in vivo studies. CCA xenografts (via mouse flank model) were generated with non-targeting small guide-bearing KMCH and sgSHP2-KMCH cells. Mice were treated with q3 day cytotoxic treatment x 3 weeks and tumors were evaluated by growth rate, weight and volume.

Results: Profiling of tyrosine phosphatase levels by RT-PCR and immunoblot demonstrated higher levels in KMCH cells compared to HuCCT-1; notably the YAP-interacting phosphatase PTPN11 (SHP2) was elevated. Consistent with the anticipated function of the phosphatases, immunoblot demonstrated lower levels of tyrosine phosphorylated YAP (p-YAPY357) in KMCH cells compared to HuCCT-1. The role of SHP2 was further probed by incubation of KMCH and HuCCT-1 cells with NSC87877 which was associated with an increase in p-YAPY357 levels and YAP co-transcriptional activity. In addition, KMCH cells demonstrated increased YAP nuclear localization following incubation with NSC87877. The effects seen with YAP tyrosine phosphorylation were paralleled in doxycycline-inducible CRISPR/Cas9 sgSHP2-KMCH cells. In HuCCT1 cells overexpressing SHP2 (WT-SHP2), pYAPY357 levels and transcriptional activity were decreased, and the localization of YAP was shifted towards the cytoplasmic compartment. Expression of a phosphatase-dead construct (C459S-SHP2) had no demonstrable effect. A deletion-reconstitution approach utilizing induced sgSHP2-KMCH cells followed by reconstitution with expression of either wild-type or phosphatase-dead constructs was associated with a decrease in p-YAP357 levels, YAP transcriptional activity, and YAP baseline nuclear localization in wild-type alone. Increased cell death was observed in KMCH cells as compared the HuCCT-1 and sgSHP2-KMCH cells incubated with gemcitabine and cisplatin. In keeping with these observations, in vivo studies demonstrated that the sgSHP2-KMCH cell lines when compared to wild type, developed tumors with faster growth rates, and subsequently these tumors were less sensitive to the combination of gemcitabine and cisplatin therapy.

Conclusion: The tyrosine phosphatase SHP2 regulates p-YAPY357 levels, YAP co-transcriptional activity, and in vivo sensitivity to current standard chemotherapy in cholangiocarcinoma.
35. THE SYSTEMIC IMMUNE-INFLAMMATION INDEX PREDICTS PROGNOSIS IN INTRAHEPATIC CHOLANGIOCARCINOMA: AN INTERNATIONAL MULTI-INSTITUTIONAL ANALYSIS
Presenter: Diamantis Tsilimigras MD | The Ohio State University

Background: Inflammation has been associated with tumor progression and poor prognosis among patients with cancer. We sought to examine whether the systemic immune inflammation index (SII) was associated with prognosis among patients following resection of intrahepatic cholangiocarcinoma (ICC).

Methods: Patients who underwent hepatectomy for ICC between 1993-2016 were identified using an international multi-institutional database. The impact of SII on overall (OS) was assessed. The performance of the final multivariable models that included clinicopathologic factors along with inflammatory markers (i.e. neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR] and SII [platelets*NLR]) was assessed using the Harrell’s concordance index.

Results: Among 821 patients, median and 5-year OS were 44 months (95% CI: 36.4-51.6) and 29.9%, respectively. Median SII was 560 (IQR 379.2-901.8) and a total of 145 (17.7%) patients presented with an elevated preoperative SII (>1,050). Patients with high SII had better OS compared with patients with low SII (median OS: 47.1 vs 17.8 months, p<0.001, Figure 1a). Similarly, high NLR (>5) and high PLR (>190) predicted better OS (both p<0.05, Figure 1b, 1c). On multivariable analysis, an elevated SII independently predicted a worse OS (HR=1.40, 95%CI 1.01-1.96), whereas high NLR (HR=1.22, 95%CI 0.85-1.77) and high PLR (HR=1.08, 95%CI 0.78-1.49) were no longer associated with prognosis. Of note, the addition of SII to the multivariable model was associated with a c-index (0.694) that outperformed models that incorporated NLR (c-index: 0.689) and PLR (c-index: 0.690) alone.

Conclusion: SII independently predicted OS among patients with resectable ICC. SII may be a better predictor of outcomes compared with other markers of inflammatory response among patients with resected ICC.
**36. TUMOR-DERIVED ORGANOID CULTURE FOR FUNCTIONAL PERSONALIZED ONCOLOGY IN CHOLANGIOCARCINOMA**

_F Schaub, U Kim, C Grandori, A Zarrinpar_

**Presenter:** Ali Zarrinpar MD, PhD | University of Florida

**Background:** Given the low incidence of tumors such as cholangiocarcinoma (CCA), it is difficult to establish the efficacy of standard treatment protocols with any certainty. This compels clinicians to select therapeutic approaches based on anecdotal evidence or small case series. The advent of tumor genetic sequencing has not resulted in substantial changes in treatment choices, as these fail to identify targets in the vast majority of cases. We have developed a high-throughput functional assay to test a library of targeted drugs against individual patient-derived tumor organoids from CCA. We seek to show the feasibility of this approach to yield experimentally-validated therapeutic options for patients.

**Methods:** Four consecutive patients with CCA who were undergoing a planned standard of care biopsy or resection were enrolled in an IRB-approved prospective pilot study. Approximately 200 mg of tumor was shipped on ice overnight to SEngine Precision Medicine for growth of tumor-derived organoid culture and analysis of drug sensitivities. Organoids were evaluated using a multi-dose response to each drug in a library of 120 FDA-approved and investigational drugs. These results were compared to all previous patients. This established both functional sensitivity and the uniqueness of each patient’s response.

**Results:** Patient characteristics such as demographics, tumor pathology, Next Generation Sequencing (NGS) recommendations, and organoid-derived drug recommendations are shown in the Table. We optimized operational logistics, assessed tumor growth rates, and measured chemosensitivity reporting timelines. All four specimens resulted in adequate growth to characterize drug sensitivities. No NGS studies performed on these tumors resulted in targeted chemotherapy recommendations. Conversely, tumor organoid assays rapidly identified selective, personalized drugs in all four cases.

**Conclusion:** We have shown the feasibility of this approach in CCA. This pilot study has facilitated the expansion process, quantified the turn-around time, and identified technical and logistic barriers for future clinical trials. Our preliminary results will inform the design of a future prospective clinical trial to establish and validate this method to select personalized cancer treatments for rare malignancies.

<table>
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<th>Study ID</th>
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<th>NGS Sensitivity Recommendations</th>
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37. STANDARDIZING DIAGNOSTIC AND SURGICAL APPROACHES TO MANAGEMENT OF BILE DUCT INJURIES AFTER CHOLECYSTECTOMY: LONG TERM OUTCOMES OF 107 PATIENTS TREATED AT A HIGH VOLUME HEPATO-BILIARY CENTER

MR Jajja, A Laboe, SS Hashmi BA Sayed, JM Sarmiento
Presenter: Mohammad Raheel Jajja MD | Emory University

Background: There is still debate regarding optimal diagnostic and surgical approaches for a patient presenting with a bile duct injury (BDI). We present the results from our standardized approach over 15 years managing more than one hundred such injuries at our institution.

Methods: Data for patients undergoing repair for bile duct injuries between January 2003 and December 2018 at Emory University were reviewed retrospectively. Demographic data and clinical notes were reviewed. Kaplan-Meir survival curves were constructed for determining primary and secondary biliary patency rates. All cases were performed solely by the senior author JMS.

Results: 123 patients underwent a biliary repair with the senior author over the study period. Of these 16 were excluded as they had BDIs secondary to previous hepatic resections. The remaining 107 consecutive patients had BDIs all secondary to cholecystectomy induced injury. Of these 42 (39%) were identified intra-op by the index surgeon, while the remaining 65 (61%) were identified in the post-operative period (median time 10 days [IQR 3-174]). 16 (15%) patients had an attempted repair of this injury and 9 (8%) patients had been noted to have a cholangiogram performed by the index surgeon. Magnetic Resonance Imaging (MRI) (n=80, 75%) with selective angiography (n=48, 45%) was the routine diagnostic approach to these patients in our clinic. ERCP (n=23, 21%) was used selectively if MR quality was suboptimal or the patient needed a therapeutic intervention. MR was omitted if cholangiogram images were available at time of consult. Bismuth I-V classification of all 107 injuries respectively: 9 (8%), 35 (33%), 30 (28%), 11 (10%), 11 (10%). Concomitant hepatic arterial injuries were identified in 30 (28%) patients (Angiography identified 28 of 28, MR identified 3 of 30, while CTA identified 2 of 16 such injuries). 15 patients had their injuries repaired within 4 days of index procedure, while the remaining had at least a 3-week interval (median time to repair 65 days [IQR 42-213]). Hepp-Couinad procedure was employed as first choice for bile duct repair (n=89, 84%). Overall 18 patients required a liver resection as part of their surgical management. 27 (25%) patients experienced a Clavien I-II and 3 (3%) experienced a Clavien III-V grade complication within 30 days. Primary patency was 100% at 30 days (Figure 1) and 91% at 15 years. Overall 10 patients required a redo-biliary anastomosis during this period.

Conclusion: Our data demonstrates that a standardized approach to diagnostic modalities reliably identified biliary and concomitant arterial injuries. We recommend that MRI be used as first imaging modality for patients suspected of having BDI and should be supplemented with angiography. ERCP use should only be considered for specific therapeutic intervention or if MR quality is subpar. The overall role of CT/CTA is limited in defining either biliary or arterial injuries. In our experience CT use should be reserved for follow-up of bile leaks or PTC placements. A standardized surgical approach, using Hepp-Couinad as procedure of choice with appropriate liver resection for BDI management can lead to greater than 90% primary patency rates at 15 years.
Figure 1. Kaplan-Meir graph demonstrating primary patency following surgical repair of bile duct injuries over first 2 years (38% follow-up at this interval)
38. NEOADJUVANT CHEMOTHERAPY FOR PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA: A PROPENSITY-SCORE MATCHED SURVIVAL ANALYSIS
O Utama, J Permuth, G Dagne, A Sanchez-Anguiano, A Allman, J Denbo, R Kim, D Anaya
Presenter: Ovie Utuama MD | Moffitt Cancer Center

Background: Although liver resection provides the only potentially-curative approach for management of intrahepatic cholangiocarcinoma (ICC), locoregional and systemic recurrence remain common. Despite recent studies supporting the use of multimodality therapy for resectable ICC, the true survival benefit in the adjuvant setting is small. Neoadjuvant chemotherapy (NC) is a potential alternative for this population, though its role for resectable disease is controversial and has not been well characterized. We sought to evaluate preoperative chemotherapy utilization across hospitals and examine the survival benefit of this approach.

Methods: We performed a retrospective cohort study of patients in the National Cancer Data Base with diagnosis of ICC and treated with curative-intent surgery (2006-2014). Patients with stage 4 disease, and those diagnosed and treated at different facilities were excluded. The study cohort included only patients with a complete case analysis, excluding those with missing relevant information (stage). A landmark approach was used to define the final study sample. NC utilization overtime was evaluated across participating hospitals, and predictors of NC use were identified using multivariable logistic regression. The effect of NC on overall survival (OS) was examined using unadjusted and propensity score-matched Cox regression models. All Cox models accounted for clustering of survival effect within hospitals.

Results: A total of 881 patients met inclusion criteria and represented the study cohort. NC was used in 8.3 % of the population. On multivariate analysis, increasing stage (P < 0.001) and year of diagnosis (P=0.03) were independent predictors of NC utilization. Median follow-up and OS for the whole population were 26.6 and 36.4 months, respectively. In the unadjusted model, there was no difference in OS in the NC versus non-NC groups for the whole population (median OS of 51.8 months versus 35.6 months, respectively; P=0.51), however there was a trend towards improved survival in the NC group for the high-risk population (stages 2-3) (median OS 35.7 versus 26.4 months, respectively; P=0.1). After adjusting using the propensity-score 1:4 matched cohort, NC utilization was associated with a non-significant trend towards improved OS (HR 0.78 [95%CI 0.54-1.11]; P=0.16).

Conclusion: Overall neoadjuvant chemotherapy utilization for resectable ICC is low, although its use has increased over time and for those with more advanced disease. Despite no clear survival benefit, this study shows that patients with more advanced disease may benefit from a multimodality approach using preoperative chemotherapy. Appropriately powered multi-institutional trials, targeting these high-risk patients, are still needed to support the systematic use of neoadjuvant chemotherapy for this population.
39. TRANSPLANTATION FOR HCC: A NATIONAL ANALYSIS OF RECIPIENT SELECTION CRITERIA  
MC Morris, AF Kassam, TC Lee, KJ Halazun, SA Shah, RC Quillin III  
Presenter: Mackenzie Morris MD | University of Cincinnati  

Background: Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy with the Milan criteria being the standard to identify and prioritize patients for liver transplantation (LT). However, many centers in the United States are now performing LT in patients beyond Milan. In this study, we evaluated the outcomes of patients within and outside of Milan at LT as well as the impact of downstaging on outcomes after LT.

Methods: The United Network of Organ Sharing (UNOS) database was queried for all patients with a diagnosis of HCC who underwent LT from 2009 to 2019. Pediatric patients and those without tumor-specific data were excluded. Patients were divided into three groups at LT: within Milan criteria (within Milan), within the University of California San Francisco (UCSF) criteria but beyond Milan (beyond Milan, within UCSF), and beyond both Milan and UCSF criteria (beyond UCSF) at the time of LT. Additionally, a subset analysis was performed for patients originally outside Milan, but within Milan or within UCSF at the time of LT. The cause of death variable was used to identify patients who died due to HCC in order to examine cause-specific survival.

Results: A total of 16,883 patients (within Milan, n=16,165; beyond Milan, within UCSF, n=535; beyond UCSF, n=183) were identified who met inclusion criteria with a median follow-up of 2.9 (1.0-5.1) years. Kaplan-Meier survival analysis revealed a decreased overall and HCC cause-specific survival in patients within and beyond UCSF compared to those within Milan (p<0.01). In multivariate analysis of overall survival adjusting for recipient and donor specific factors, beyond Milan criteria, AFP &gt; 90 mg/dL, and liver-directed therapy were associated with increased risk of death (Figure - black). In multivariate analysis for HCC cause-specific survival, beyond Milan criteria, AFP &gt;90 mg/dL, and liver-directed therapy were associated with increased risk of death (Figure – grey). Finally, a subset analysis revealed no difference in overall survival in patients who were always within Milan (3-year survival of 82%) compared to those originally outside Milan but downstaged to within Milan (78%) or within UCSF at the time of LT (82%, p=0.44).

Conclusion: UCSF criteria have been increasingly proposed to allow for expansion of patients who are able to undergo liver transplantation, but this expansion is not without risk of worse survival. However, patients who are down-staged to within UCSF may have similar results to those always within Milan or those down-staged to within Milan.

![Graph](image-url)
40. SERUM AXL/GAS6 ALLOWS PREDICTION OF ONCOLOGICAL OUTCOME IN PATIENTS SUFFERING FROM HEPATOCELLULAR CARCINOMA UNDERGOING CURATIVE LIVER RESECTION

Ortmayr, D Pereyra, C Köditz, J Santol, B Rumpf, J Fuxsteiner, W Mikultis, P Starlinger

Presenter: Patrick Starlinger MD | Mayo Clinic, Rochester

Background: Receptor ligand pair Axl-Gas6 is involved in liver homeostasis directing innate immunity, tissue repair and regeneration. Dysbalanced signalling has been implicated in various liver diseases. Experimental data expounds their pathological value in progression of steatohepatitis and liver fibrosis as well as in the oncological setting. Overexpression actuates hepatic inflammation and HSC activation, as well as tumor growth and metastatic potential, indicating predictive value of Axl and Gas6. Recent studies have demonstrated high diagnostic accuracy of soluble Axl in detection of advanced stage liver fibrosis, cirrhosis and early HCC. Furthermore, Axl tissue levels were found to be associated with poor oncological outcome. Within this study we aimed to evaluate the predictive potential of Axl-Gas6 in terms of postoperative clinical and oncological outcome in patients undergoing liver resection.

Methods: A total of 166 patients suffering from either primary liver malignancies or liver metastasis were included in this study. Serum samples were collected prior to liver resection. Measurement of soluble Axl/Gas6 levels was performed via ELISA. Postoperative performance (liver dysfunction (LD) and morbidity) and oncological outcome (overall survival (OS) and disease free survival (DFS)) were recorded. In particular, liver dysfunction (LD) was assessed using the ISGLS criteria and postoperative complications were graded according to Dindo et al.. Grades of morbidity >2 were classified as “severe morbidity”.

Results: LD was found to be significantly associated with elevated Axl/Gas6 levels (both P < 0.001). To assess their preoperative predictive value ROC analysis was performed, revealing a significant association of preoperative Axl/Gas6 levels and clinical outcome with an area under the curve (AUC) of 0.68 and 0.74. According to the Youden Index cut-off values were set for Axl/Gas6 - 41.73 and 30.76 respectively, identifying the subset of patients facing significantly worse clinical outcome in terms of LD and morbidity (all P < 0.001). Also DFS was found to be shorter in patients with elevated Axl/Gas6 levels. However this difference was not statically significant (P=0.063). In line with these results patients with elevated Axl/Gas6 levels had significantly worse 1 year survival rates (Axllow – Axlh 91.3% vs 71.91%, p=0.006 and Gas6low – Gas6high 92.86 % vs 72.55%, p=0.002).

Conclusion: Within the present study we identified Axl/Gas6 as valuable tools to predict patients risk for postoperative morbidity, early disease recurrence and ultimately shortened OS. The fact that Axl/Gas6 levels seemed to be associated with shorted DFS might account for the close association of Axl/Gas6 with patients overall survival after liver resection. Evaluation of these pathophysiologically important molecules might improve clinical decision making in patients prior to liver resection.
41. FRAILTY AS A PREDICTOR OF POSTOPERATIVE OUTCOMES FOLLOWING LIVER RESECTION

T Bao, L Ruo, M Fabbro, PE Serrano

Presenter: Tyler McKechnie BSc | McMaster University

Background: Frailty, defined as a state of decreased physiologic reserve, characterized by a loss of resiliency in the face of acute stress is a condition that is frequently encountered by liver surgeons. We sought to evaluate frailty as a predictor of postoperative complications following liver resection using the modified frailty index (mFI).

Methods: This is a retrospective cohort study of consecutive adult patients undergoing liver resection between 2011 and 2018 at a single academic institution. An mFI consisting of 11 variables adapted for the National Surgical Quality Improvement Program database from the Canadian Study of Health and Aging Frailty Index was used. These variables have been previously validated and include patient comorbidities and functional abilities. Patients were stratified into two groups, high mFI (≥0.27) and low mFI (< 0.27). Postoperative complications were graded using Clavien-Dindo. The effect of mFI on postoperative complications and 90-day mortality was evaluated using multiple logistic regression and expressed as odds ratio (OR) and 95% confidence interval (CI).

Results: Among 409 liver resections, there were 58/409 (14%) patients with a high mFI (mFI ≥0.27). Low mFI patients were significantly younger (63 vs. 70 years, p<0.001) and more likely to meet >4 METS (90% vs. 60%, p<0.001). There were no differences between the high versus low mFI group in the type of liver resection performed, open (37% vs. 35%) or laparoscopic (57% vs. 55%), in the number of liver segments resected (3 vs. 4, p=0.417) or in the operative room time (257 vs. 293 min, p=0.097), respectively. Median length of hospital stay was significantly longer for the high mFI group (9.5 vs. 5 days, p<0.001). When compared to patients with low mFI, patients with a high mFI had a significantly higher proportion of postoperative complications (79% vs. 46%, p<0.001). This was true for minor complications (69% vs. 42%, p<0.001), major complications (50% vs. 13%, p<0.001) and 90-day postoperative mortality (12% vs. 3.4%, p=0.04). By multivariate analysis, longer operating time, per 30-minute increase (OR 1.15, 95%CI 1.03 to 1.27), higher number of liver segments resected (OR 1.43, 95%CI 1.12 to 1.82), and high mFI, per unit increase (OR 6.74, 95%CI 2.76 to 16.51) were independent predictors for the development of major complications and 90-day mortality.

Conclusion: The mFI predicts postoperative outcomes following liver resection and can be used as a risk stratification tool for patients being considered for surgery.
42. DEVELOPMENT AND VALIDATION OF A NOVEL MODEL TO PREDICT LYMPH NODE METASTASIS AMONG PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA


Presenter: Amika Moro MD | The Ohio State University

Background: The accuracy of preoperative imaging to assess the status of the nodal basin among patients with intrahepatic cholangiocarcinoma (ICC) remains relatively low. We sought to develop and validate a model to predict the likelihood of occult lymph node metastasis (LNM) among patients with resected ICC.

Methods: Patients who underwent hepatectomy for ICC between 1990-2016 with data on pathological LN status were identified using a multi-institutional database. The cohort was randomly divided into a training- and validation-set. Clinicopathological data were assessed and a model was developed based on the lowest Akaike information criterion (AIC) in the training set followed by assessment of the model in the validation set. An online calculator was developed based to estimate the risk of LNM.

Results: Among 843 patients who underwent resection of ICC, 198 (23.5%) individuals had at least one LNM identified on final pathology. Preoperative variables associated with LNM included sex (male: odds ratio [OR] 2.91; 95%CI 1.65-5.15), LN status on preoperative imaging (suspicious: OR 8.93; 95%CI 4.56-17.5, metastatic: OR 8.83; 95%CI 3.77-20.7), morphologic sub-type (mass-forming + intraductal growth vs periductal infiltrating, OR 7.45; 95%CI 3.31-16.78), preoperative carcinoembryonic antigen (CEA) level (OR 1.40; 95%CI 1.09-1.80), low albumin level (OR 1.69; 95%CI 1.08-2.65), as well as number of nodules (OR 1.27; 95%CI 0.96-1.70). A model based on these preoperative factors had a sensitivity of 81% with a 69% specificity to predict LNM. The positive and negative predictive values associated with the model were 0.45 and 0.92, respectively, with an accuracy of 72%. The Harrell's concordance index (c-index) was 0.84 and 0.83 in the training and validation sets, respectively. An online calculator to estimate the likelihood of LNM was developed for use in the clinical setting (https://medicalcal.shinyapps.io/ICC_LNM/) (Figure)

Conclusion: Preoperative estimation of LNM can be enhanced utilizing an online calculator that incorporates various clinical, morphologic, and tumor specific factors. Such a tool may guide surgeons in assessing patients for treatment with preoperative therapy, as well as lymphadenectomy at the time of surgical resection of ICC.
Prediction of Node Positive Disease in Intrahepatic Cholangiocarcinoma

Number of tumor nodule:
1

CEA at diagnosis (ng/ml):
2.5

Serum albumin (g/dL):
3.5

Sex:
Male

Morphologic type:
Mass-forming or Intraductal growth

Preoperative lymph node status on imaging:
Negative

Probability of Positive Lymph Nodes on Pathology:
7.3%

*Performance metrics of this calculator:
Sensitivity: 0.81, Specificity: 0.69, PPV: 0.45, NPV: 0.92, Accuracy: 0.72
Background: NSQIP database was developed as a risk calculator to help surgeons and patients to decide regarding surgical treatment. Purpose of this study was to determine the accuracy of current risk calculator for patients who underwent hepatectomy and whether the predictive accuracy varied with age.

Methods: Using NSQIP database, patients who underwent hepatectomy between 2012 and 2015 were included to the analysis. Patients with current procedural terminology (CPT) code for right hepatectomy, left hepatectomy and trisegmentectomy were categorized as major hepatectomy. Analysis of variance was performed to assess differences between three age categories (18-64 years, 65-79 years, and 80-89 years) in predicted and actual mortality and Pearson correlation coefficients were calculated. Logistic regression models were constructed to evaluate associations adjusted for key covariates (BMI, race, smoking, functional status, and major hepatectomy).

Results: A total of 10956 patients were included with age distribution of 18-64 (n=6924, 63.2%), 65-79 years (3586, 32.7%), and 80-89 (n=446, 4.1%). About one-third (n=4082, 37.3%) of patients underwent major hepatectomy. Both actual and predicted mortality increased with age (P < 0.001) (Figure). The overall correlation between actual and predicted mortality was low (r=0.25, P < 0.001). This correlation was weakest in the oldest age group (80-89 years) for partial hepatectomy (r=0.06, P=0.28). After adjusting for covariates the interaction term between age and predicted mortality was statistically significant, indicating the varying accuracy of the actual and predicted mortality by age. Both predicted and actual morbidity increased with age and predicted morbidity was considerably overestimated across all age groups. The strongest correlation was seen between actual and predicted morbidity in age group of 65-79 years among patients who underwent major hepatectomy (r=0.25, P < 0.001).

Conclusion: The ACS NSQIP risk calculator in older patients appears to overestimate overall mortality and morbidity risk, especially for patients undergoing major hepatectomy procedure. In elderly patients undergoing liver resection, functional assessment in addition to NSQIP calculator may aid in a more accurate risk prediction.
44. CARE FRAGMENTATION AND FAILURE TO RESCUE IN READMISSIONS FOLLOWING HEPATOPANCREATOBILIARY AND GASTRIC ONCOLOGIC SURGERY: SURGICAL VOLUME AT THE REAMDISSON HOSPITAL IS ASSOCIATED WITH MORTALITY

D Brauer, N Wu, M Keller, C Hammill, R Fields, W Hawkins, D Sanford

Presenter: David Brauer MD, MPHS | Washington University, St. Louis

Background: The surgical management of hepatopancreatobiliary (HPB) and gastric malignancies regularly occurs at major referral centers and is associated with a high rate of postoperative readmissions. Prior studies have shown that care fragmentation following surgery, including readmission to a hospital other than the index surgical hospital (an ‘outside hospital’ (OSH)), is associated with worse outcomes. No prior study has examined hospital-level variables associated with outcomes following readmission in this patient population.

Methods: Patients undergoing HPB or gastric oncologic surgeries were identified from select State Inpatient Databases from the Healthcare Cost and Utilization Project from 2006-2014. Follow-up occurred up to the earliest of 90 days after discharge, receipt of chemotherapy, or discharge to hospice. The primary outcome was readmission mortality, with secondary outcomes of total readmission inpatient cost and total readmission inpatient length of stay. Annual hospital surgical volume was calculated using HCUP data for oncologic and non-oncologic HPB and gastric surgeries. Additional hospital-level variables were linked using the American Hospital Association Annual Survey Database. Due to data use agreements, hospitals with less than 10 visits during the inclusion period were excluded. Kruskal-Wallis test, logistic regression, and Youden’s index were used.

Results: 31,526 patients were discharged following HPB or gastric oncologic surgery. 7,536 (24%) were readmitted within 90 days to a total of 636 hospitals. 28% of readmissions (n=2,124) were to OSH. For patients readmitted to OSH, 90-day postoperative mortality was 50% higher than mortality for patients readmitted to the index surgical hospital (8.0% vs 5.4%; OR 1.5, 95% CI 1.2 – 1.9). Looking solely at the hospital the patient was readmitted to, 188 hospitals had 10 or more readmissions during the inclusion period, accounting for 75% of all readmissions. Hospital size, measured by bed count, was not associated with readmission mortality, cost, or length of stay. However, a hospital’s annual volume of HPB and gastric surgeries was associated with readmission mortality; patients were 37% more likely to die during their readmission if they were readmitted to a hospital with less than 100 combined annual HPB and gastric procedures (6.4% vs 4.7%; OR 1.37, 95% CI 1.1 – 1.7). When comparing large volume (100 or more procedures annually) and small volume hospitals, total 90-day readmission inpatient cost was 23% higher at large volume hospitals (median $15,000 vs $12,000; p<0.01). This could be a reflection of the costs of achieving rescue through surgical intervention, as significantly more surgeries were performed at larger hospitals (8.3% vs 5.3%, p<0.01). Total 90-day readmission length of stay was no different between the groups (median 6 days; p=0.82).

Conclusion: Alongside sound clinical judgement, this data should be used to inform the decision-making process for where a patient should be readmitted following HPB and gastric surgery. To promote successful rescue after complications and readmission following surgery, efforts should be made to reduce care fragmentation and to direct readmissions to hospitals performing 100 or more annual HPB and gastric surgeries.
45. LONG-TERM DEPENDENCY OUTCOMES IN OLDER ADULTS FOLLOWING HEPATECTOMY AND PANCREATECTOMY FOR CANCER: A POPULATION-BASED ANALYSIS

S Bennett, TR Chesney, NG Coburn, B Haas, V Zuk, AL Mahar, AT Hsu, H Zhao, I Menjak, D Manuel, D Gandell, FC Wright, J Hallet

Presenter: Sean Bennett MD | University of Toronto

Background: By 2030, older adults (OA) (>70 years old) will comprise nearly 75% of incident cancers. Functional outcomes are central to decision-making by OA, but long-term risks of dependency following cancer surgery have not been described beyond 1 year in this population. We evaluated healthcare dependency by examining homecare use and institution-free survival (IFS) following hepatectomy and pancreatectomy for cancer in OA.

Methods: A population-based analysis of patients > 70 years old undergoing hepatectomy and pancreatectomy for cancer between 2007-2017 using linked administrative datasets. Outcomes were 1) receipt of homecare and 2) IFS, defined as < 14 days in healthcare institutions within one year. For IFS, institution-days included any day spent in emergency or inpatient acute care, outpatient procedures, inpatient mental health care, inpatient rehabilitation, or skilled nursing facilities. We used time-to-event analyses accounting for competing risk of death. Homecare was analyzed with cumulative incidence functions accounting for competing risks of death and nursing home admission, and Andersen-Gill multivariate models, and IFS with Kaplan-Meier methods and Cox multivariate models. Analyses were stratified by hepatectomy and pancreatectomy procedures.

Results: Of 2268 patients, 982 (43.3%) underwent hepatectomy, 1283 (56.6%) pancreatectomy, and 83 (3.6%) combined resection. Homecare use was highest (72.3% of eligible patients) in post-operative month-1 and subsequently decreased to stabilize at a new baseline after year-1 (25.5%) and year-5 (18.3%). Female sex (HR 1.18, 95%CI 1.05-1.32), receiving adjuvant therapy (HR 1.56, 95%CI 1.37-1.78), and more recent year of surgery in 2012-2017 (HR 3.80, 95%CI 3.05-4.72) were associated with increased hazards of receiving post-operative homecare. The ratio of home nursing care vs. personal support services reversed from 68%/26% in year-1, to 29/64% respectively in year-5. IFS dropped most in year 1 but stabilized over years 2 to 5. IFS at 1 and 5 years were 40.6% (95%CI 38.5%-42.6%) and 28.1% (95%CI 25.9%-30.3%), respectively. The ratio of institution-days in acute care vs. nursing homes went from 77%/14% in year-1 to 23%/70% in year-5. Factors such as duodenum (HR 1.45, 95%CI 1.15-1.70) and pancreas (HR 1.20, 95%CI 1.02-1.42) cancer and rural residence (HR 1.24; 95%CI 1.04-1.48) were independently associated with inferior IFS, and recent diagnosis year in 2012-17 (HR 0.84; 95%CI 0.76-0.93) and perioperative systemic/radiation therapy (HR 0.88; 95%CI 0.78-0.99) with superior IFS. Increasing age was neither associated with homecare receipt nor IFS. Trends in outcomes were similar for hepatectomy and pancreatectomy patients, but with higher healthcare dependence following pancreatectomy.

Conclusion: Following HPB cancer surgery, there is a high rate of long-term healthcare dependency for OA. First, there is immediate high need for homecare that reaches a new baseline after 6 months, indicating a new state of healthcare dependence focused on personal support services. Second, the majority of OA will spend over 2 weeks annually in institution following surgery, with the greatest loss in IFS incurred in the first year. These findings are important patient-centred findings. They outline the need for greater pre-operative preparation and transitional care planning, which can be tailored by risk factors identified herein and individual prognostication tools to further support clinical practice.
**46. A YEAR IN THE LIFE OF AN HPB FELLOW: TRACKING TRENDS IN CASE COMPLEXITY, OPERATIVE AUTONOMY, AND MIS APPROACHES OVER THE PAST 8 YEARS**

*J Weis, D Jeyarajah, M Majella Doyle, D Scott, P Polanco, J Tellez, A Alseidi*

**Presenter:** Joshua Weis MD | University of Texas Southwestern Medical Center

**Background:** Hepatopancreaticobiliary (HPB) Surgery is a complex field that demands advanced training to ensure favorable outcomes for patients. The Fellowship Council (FC) is a major accrediting organization that oversees more than 150 fellowships across multiple disciplines. For more than a decade, the AHPBA has partnered with the FC to offer high quality fellowships in HPB surgery. The primary aim of this study was to review FC case logs to define trends in HPB fellows’ volume of index cases, use of minimally invasive approaches, and level of operative autonomy over time.

**Methods:** We obtained case log data for all FC fellows trained from 2007-2019 (12 academic years). From 2007-2011, there were fewer than 20 HPB fellows per year, so data from these years were excluded from analysis. We identified 81 complex HPB (non-transplant) case codes and divided them into 5 index case categories including 1.) Major hepatectomy (≥2 segments), 2.) Major anatomic hepatectomy, 3.) Whipple procedure (pancreaticoduodenectomy), 4.) Major pancreas operation (including Whipple), and 5.) Major biliary operation (does not include cholecystectomy). The distribution of cases done using minimally invasive surgical (MIS) approaches (i.e. laparoscopy or robotics) were calculated for each year. To analyze changes in autonomy level, we calculated the share of HPB cases logged as primary surgeon or teaching assistant in each academic year. Median volumes in each index category were compared over time using Kruskall Wallis tests. Use of MIS approaches and level of autonomy were analyzed using linear regression analysis. For all statistical analyses p<0.05 was considered significant.

**Results:** For the 8 years analyzed, 246 fellows logged 24,878 operations. The median volume of HPB cases overall and within each index category did not change significantly over time (Figure). Each year, approximately half of hepatectomy cases logged by HPB fellows were major anatomic resections, and more than half of the major pancreatic cases logged were Whipple procedures. The share of cases performed with MIS approaches exhibited slow linear growth from 13.9% of all major HPB cases in 2012 to 19.4% in 2019 (r=0.85, p<0.01). Operative autonomy decreased over time as the proportion of cases logged as primary surgeon or teaching assistant (TA) exhibited linear decay from 94.4% of all cases in 2012 to 84.1% of cases in 2019 (r=0.86, p<0.01).

**Conclusion:** Over the past 8 years, HPB Fellowships have consistently offered substantial volumes of hepatic, pancreatic, and biliary index cases. The use of MIS techniques is increasing; however, operative autonomy seems to be declining. HPB programs may need to explore faculty development initiatives to increase attending surgeons’ comfort with providing operative autonomy.
Median Index Cases Per Fellow 2012-2019 Academic Years

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<td>41</td>
<td>37.5</td>
<td>37</td>
<td>39</td>
<td>39</td>
<td>38.5</td>
<td>43</td>
<td>36</td>
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<tr>
<td>Major Anatomic Hepatectomy</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>20.5</td>
<td>21</td>
<td>19</td>
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<td>Whipple</td>
<td>19</td>
<td>19.5</td>
<td>23</td>
<td>23</td>
<td>23.5</td>
<td>26</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Major pancreas</td>
<td>33</td>
<td>31.5</td>
<td>37</td>
<td>34</td>
<td>37</td>
<td>43</td>
<td>41.5</td>
<td>44</td>
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<tr>
<td>Major Biliary</td>
<td>14</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>15</td>
<td>11</td>
<td>14.5</td>
<td>10</td>
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<tr>
<td>All Major HPB</td>
<td>78</td>
<td>68.5</td>
<td>69</td>
<td>73</td>
<td>77</td>
<td>75.5</td>
<td>78</td>
<td>80</td>
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47. SETTING MASTERY STANDARDS IN HEPATO-PANCREATO-BILIARY SURGICAL ULTRASOUND
E Hagopian, R Yudkowsky
Presenter: Ellen Hagopian MD | Hackensack Meridian School of Medicine at Seton Hall University

Background: A standardized curriculum in Hepato-Pancreato-Biliary (HPB) ultrasound (US), grounded in a Mastery skills framework, was developed in 2014 for HPB fellows in Americas Hepato-Pancreato-Biliary Association-Fellowship Council accredited programs. We previously developed two assessment tools for laparoscopic (LAPUS) and open US (IOUS) in HPB Surgery, each of which contains 14 items (skills) and a global performance item, using the O-Score entrustment scale, in which 1="I had to do it", 2="I had to talk them through", 3="I had to prompt them from time to time"; 4="I needed to be in the room just in case" and 5="I did not need to be there." A formative skills practicum utilizing these tools is offered annually to HPB fellows approaching graduation to provide individual performance feedback. The aim of this work was to establish Mastery standards for our two assessments, and to apply those standards to a sample of graduating fellows, providing consequential validity evidence within Messick’s framework.

Methods: Standard setting: Faculty with expertise in HPB Surgery and HPB US from the membership of Americas Hepato-Pancreato-Biliary Association participated in standard setting exercises. Faculty were asked to rate each item and global US performance for both IOUS and LAPUS: What is the probability that a graduating HPB fellow, who is well-prepared for independent practice, is able to perform this skill? Please rate as a percentage. Item-level Mastery Angoff cut scores were determined as the mean rating across all judges. The overall Mastery Angoff cut score was determined as the mean cut score across all items. Mastery Angoff cut scores were converted to the 5-point entrustment scale (i.e., cut score*5). Fellow performance: At the 2019 annual US skills practicum, fellow performances were evaluated using the assessment tools and the Mastery Angoff standards. This study met criteria for exemption by the University of Illinois-Chicago Institutional Review Board (2019-0265).

Results: A total of 15 faculty were invited to participate, 12 of whom returned the questionnaire. To account for outliers, the highest and lowest faculty ratings were removed, thus standards were based on 10 faculty experts. For IOUS, the overall mean cut score across all items was 91.48% (SD 0.04) and for LAPUS, the overall mean cut score across all items was 89.96% (SD 0.04). The mean global IOUS performance cut score was 96.00% (SD 0.07), whereas the mean global LAPUS performance cut score was 87.80% (SD 0.14). (See Table) A total of 13 of 18 fellows who participated in the 2019 US skills practicum agreed to have their de-identified data evaluated. Overall, fellows did not meet standards in 11/14 IOUS items and in 13/14 LAPUS items. The mean global performance entrustment score was 3.62 (SD 0.65, range 2-4) in IOUS and 3.62 (SD 0.77, range 2-5) in LAPUS, which did not meet the entrustment standards of 4.80 and 4.39, respectively.

Conclusion: AHPBA-FC HPB fellows prior to graduation are not meeting Mastery Standards for HPB US performance determined by a panel of expert faculty. A change in educational policy or curriculum may be needed to improve fellow performance.
<table>
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<tr>
<th>Mastery Angoff ACROSS ALL SKILLS</th>
<th>IOUS Cut score based on faculty ratings (n=10), mean (SD)</th>
<th>IOUS Fellow Performance based on Entrustment Score (n=13), mean (SD)</th>
<th>LAPUS Cut score based on faculty ratings (n=10), mean (SD)</th>
<th>LAPUS Fellow Performance based on Entrustment Score (n=13), mean (SD)</th>
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<tbody>
<tr>
<td>Mastery Angoff ACROSS ALL SKILLS</td>
<td>91.48% (0.04)</td>
<td>N/A</td>
<td>89.96% (0.04)</td>
<td>N/A</td>
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<td>Entrustment ACROSS ALL SKILLS</td>
<td>4.57</td>
<td>4.21 (0.48)</td>
<td>4.5</td>
<td>4.12 (0.67)</td>
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<tr>
<td>Mastery Angoff GLOBAL</td>
<td>96.00% (0.07)</td>
<td>N/A</td>
<td>87.80% (0.14)</td>
<td>N/A</td>
</tr>
<tr>
<td>Entrustment GLOBAL</td>
<td>4.80</td>
<td>3.62 (0.65)</td>
<td>4.39</td>
<td>3.62 (0.77)</td>
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48. VARIATION IN INPATIENT OPIOID CONSUMPTION FOLLOWING HEPATOPANCREATIC SURGERY
A Paredes, J Hyer, M Dillhoff, A Ejaz, J Beane, J Cloyd, A Tsung, T Pawlik
Presenter: Anghela Paredes MD, MS | The Ohio State University

Background: Variation in inpatient opioid consumption among patients undergoing hepatopancreatic surgery remains poorly defined. We sought to examine the variability in inpatient opioid consumption following hepatopancreatic surgery and determine the association between high inpatient opioid use and post-discharge outcomes.

Methods: All hepatopancreatic cases performed at a single tertiary-care institution between 2015 and 2018 were identified using Current procedure Terminology codes. Only patients older than 18 years of age, who were prescribed an opioid during inpatient surgical admission and at time of discharge were included in the final analytic cohort. High inpatient opioid consumption was defined as greater than the 75th percentile of average daily oral morphine equivalent (OME) intake.

Results: Among 891 patients who met inclusion criteria, most individuals underwent a pancreatectomy (n=488, 54.8%), whereas 403 (45.2%) patients underwent a hepatectomy. Median patient age was 63 years (IQR: 55-71), roughly one-half of patients (n=461, 51.7%) were male, and the median comorbidity burden was 7 (IQR 5-8). The average daily OME was 53 (IQR 25-105). Patients with high inpatient opioid consumption were more likely to be younger (57, IQR 50-66 vs 65, IQR 57-72, p<0.05); in contrast, Charlson Comorbidity burden score (6 IQR 5-8 vs 7 IQR 5-8) and sex (male: 54.2% vs 50.9%) were not associated with high opioid consumption (p>0.05). Individuals with high inpatient opioid consumption were, however, more likely to be readmitted following surgery (high OME: n=90, 40.0% vs. low OME: n=157, 23.6%). Compared with individuals with low OME consumption, the median OME prescribed at discharge was 225 OMEs more among patients with high inpatient opioid intake (p<0.05). On multivariable analysis, after adjusting for age, sex, length of operation, comorbidity burden and type of operation, individuals with high inpatient opioid consumption had more than a two-fold increased risk of readmission within 30-days (OR: 2.17, 95%CI 1.55-3.05).

Conclusion: Among patients undergoing hepatopancreatic surgery, high variability exists in inpatient opioid consumption within the same institution. High inpatient opioid consumption was associated with adverse post-discharge outcomes such as readmission. Providers and patients need to be aware of the adverse consequence of high inpatient opioid consumption.
V 8. ROBOTIC ALPPS FOR MULTIPLE COLORECTAL LIVER METASTASES  
MA Machado, RC Surjan, FF Makdissi  
Presenter: Marcel Machado MD | University of Sao Paulo

**Background:** The ALPPS procedure is a useful strategy to treat patients with advanced liver tumors and small future liver remnants. There are only two reports of robotic ALPPS in the literature. In the first report, only the second stage was completed using the robotic approach, whilst in the second description, only the first stage was completed using the robotic platform. This video presents a robotic ALPPS procedure to treat synchronous colorectal liver metastases. To our knowledge, this is the first case of robotic ALPPS in which both stages were completed using the robotic approach.

**Methods:** A 71-year-old man with synchronous liver metastases from a sigmoid cancer was referred for treatment. A multidisciplinary team decided to use chemotherapy followed by liver resection (first), then colon resection. After 4 cycles, an objective response was observed. A multidisciplinary team decided to use the ALPPS procedure. The future liver remnant (segments 3, 4 and Spiegel lobe) was calculated to be 24% and the robotic approach was proposed. Colon resection was performed after the ALPPS procedure, also using robotic approach. Xi da Vinci system was used in all operations.

**Results:** The operative time for the first stage was 293 minutes. The patient recovered well and was discharged on the fourth day. The second stage operative time was 245 minutes. Recovery was uneventful and the patient was discharged on the fourth postoperative day. Finally, the patient underwent robotic resection of the primary colorectal neoplasm. The operative time was 182 minutes, recovery was uneventful, and the patient was discharged on the 5th postoperative day. Final pathology disclosed a T3N1bM1 adenocarcinoma. Liver pathology confirmed the colorectal metastases with partial response. All surgical margins were free. The patient is well, with no signs of disease 4 months post-procedure.

**Conclusion:** Robotic ALPPS is feasible and safe. The robotic approach may have some advantages over laparoscopic and open ALPPS. This video may help oncological surgeons to perform this complex procedure.
V 9. LAPAROSCOPIC ALPPS PROCEDURE AFTER FAILED PORTAL VEIN EMBOLIZATION
M D’Hondt, L Baekelandt
Presenter: Mathieu D’Hondt | Groeninge Hospital Kortrijk

**Background:** Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) is a relatively new surgical technique for the resection of colorectal liver metastases (CRLMs) with insufficient future liver remnant (FLR). Only 27 cases of laparoscopic ALPPS have been reported in literature. This video aims to demonstrate our first experience with this minimally invasive approach.

**Methods:** In January 2016 a 51 year old male patient presented with massive bilobar colorectal liver metastases. There was one CRLM in the left hemiliver and numerous CRLMs in the right hemiliver. The primary tumor was asymptomatic and the patient received 4 cycles of chemotherapy (Folfox/Panitumumab). Since the left hemiliver (=FLR) was only 16% of total liver volume (TLV) a right PVE (portal vein embolization) was performed. However, PVE failed and 4 weeks after PVE the FLR-volume was only 18% of TLV. Chemotherapy was continued till 12 cycles. The option of performing an ALPPS procedure was discussed with the patient and the patient agreed. First, a laparoscopic sigmoid resection was performed in October 2016. On December 12 2016 the first step of the ALPPS procedure was performed. During the first stage a metastasectomy in the left hemiliver was performed and the liver parenchyma between the left and right hemiliver was transected. Intraoperative ultrasound revealed residual portal flow in the right hemiliver after PVE. The right portal vein was isolated and transected using a vascular stapler. Eight days postoperatively the volume of the left hemiliver was 30%. The second stage of ALPPS was performed 1 day later (9 days after the first stage).

**Results:** Operative time of stage one was 300 minutes and blood loss was 150 ml. Postoperative course was uneventful and hospital stay was 4 days. Operative time of stage two was 90 minutes and blood loss was 150 ml. Postoperatively the patient developed grade A liver failure. The patient was discharged on postoperative day 8. At 20 months postoperatively there was no evidence of disease recurrence.

**Conclusion:** Laparoscopic ALPPS appears to be feasible in experienced hands. The well-recognized advantages of laparoscopy may play a favorable role in the management of patients with bilobar CRLMs candidate for an ALPPS procedure.
V 10. LAPAROSCOPIC PANCREATIC HEAD PRESERVING DUODENECTOMY THE PARENCHYMAL SPARING ALTERNATIVE TO A WHIPPLE
EA Vega, O Salehi, D Nicolaescu, S Krishnan, C Stallwood, O Kozyreva, HJ Asbun, C Conrad
Presenter: Eduardo Vega MD | Saint Elizabeth's Medical Center, Tufts University

**Background:** When endoscopic options fail, laparoscopic pancreatic head preserving duodenectomy (LPHPD) for benign duodenal lesions is a parenchymal sparing and safe alternative to a Whipple. For premalignant duodenal polyps and adenomas too large to remove endoscopically, LPHPD may be the optimal “amount” of surgery. Such lesions are at risk for undertreatment (partial endoscopic resection associated with recurrence) or overtreatment (Whipple associated with significant morbidity and unnecessary loss of functional pancreatic parenchyma).

**Methods:** A 80-year-old healthy female patient was diagnosed on endoscopy with 2 flat, symptomatic adenomas (7cm D2; 2cm D3). She had no family history of polyposis and germline testing, tumor markers and colonoscopy did not show any abnormality.

**Results:** With the patient in French position, a wide laparoscopic Kocherization was performed past IVC and aorta. Following prepyloric gastric transection the duodenum was carefully dissected off the pancreas. After transection of the proximal jejunum, a two-layer duct-to-mucosa ampullary-jejunal anastomosis and a gastrojejunostomy were performed.

**Conclusion:** LPHPD avoids under- or overtreatment of benign duodenal lesions unamendable to an endoscopic approach. If the stepwise approach described in this video is followed, LPHPD represents a parenchymal-sparing alternative to pancreaticoduodenectomy for benign duodenal lesions with reduced morbidity.
V 11. LAPAROSCOPIC COMMON BILE DUCT EXPLORATION FOR STONE ASSOCIATED WITH SURGICAL FOREIGN BODY

M Bonds, S Deal, A Alseidi
Presenter: Morgan Bonds MD | Virginia Mason Medical Center

Background: Choledocholithiasis is a common problem that presents to hepatopancreatobiliary surgeons. As more patients undergo procedures that alter the anatomy of the proximal gastrointestinal tract, common bile duct exploration emerges as one of the few options to treat these patients. Laparoscopic common bile duct exploration has been shown to shorten hospital length of stay in these situations. In this video we present a patient who has undergone a cholecystectomy and roux-en-y gastric bypass and presented with choledocholithiasis that appeared to be associated with a surgical clip.

Methods: Our patient is a 61 year old woman who presented with acute onset epigastric pain. On computed tomography, a stone was visualized within the distal common bile duct. This stone appeared to be surrounding a hyperdense foreign body consistent with a surgical clip. She had previously undergone a cholecystectomy and roux-en-y gastric bypass that was complicated by an ulcer perforation requiring resection of the gastric remnant. Double balloon endoscopy was attempted to access the common bile duct but was not successful. Surgery was consulted for laparoscopic common bile duct exploration.

Results: The video presents the key steps for performing laparoscopic common bile duct exploration which includes choledochotomy, performing choledochoscopy to locate the pathology, stone extraction and closure of the choledochotomy. We were able to identify the offending stone on choledochoscopy and it was removed. No foreign body or mucosal erosion was seen within the duct. The choledochoscopy was closed primarily without a drain as an internal drain would not be retrievable with her altered anatomy. She had a bile leak controlled by her peritoneal drain in the immediate postoperative period but this resolved within the first week and her drain was removed on postoperative day 7.

Conclusion: Laparoscopic common bile duct exploration is a safe and effective method of treating choledocholithiasis in patients with altered anatomy in the setting of a suspected foreign body within the duct. Closure of the choledochotomy should be individualized to the patient and clinical scenario. This technique should be considered to shorten the length of stay for all patients with choledocholithiasis.
V 12. ROBOTIC PANCREATICoduodenectomy AFTER UNSUSPECTED DOUBLE PERFORATION (BILE DUCT AND PORTAL VEIN) DURING ENDOSCOPIC BILIARY STENT PLACEMENT

FF Makdissi, RC Surjan, JC Ardengh, MA Machado

Presenter: Fabio Makdissi MD | Hospital Nove de Julho

Background: Endoscopic placement of biliary stent (ERCP) is a common procedure used in malignant jaundice patients. However, sometimes the cannulation of the bile duct fails, and an alternative is to perform a choledochoduodenal fistula (infundibulotomy) to access the biliary tract and place a biliary stent. We present a robotic pancreaticoduodenectomy performed after a complicated ERCP that required emergency laparotomy for drainage. The initial diagnosis was duodenal perforation. During the definitive operation, an unsuspected double perforation (bile duct and portal vein) was found and successfully treated.

Methods: A 57-year-old woman presented with progressive jaundice. ERCP disclosed a 2-cm tumor in the ampulla but cannulation of the biliary duct through the papilla failed. A choledochoduodenal fistula (infundibulotomy) was performed. A plastic endoprosthesis was inserted. Immediate after this procedure, patient developed diffuse peritonitis, leading to emergency laparotomy. Duodenal perforation was suspected but perforation site was not identified. Drain was placed. Drainage ceased after 3 weeks, drain was removed, and patient was transferred to our care. Multidisciplinary team decided for upfront pancreaticoduodenectomy. Robotic approach was proposed, and consent was obtained. Da Vinci Xi robotic system was used. Operation begins with division of adhesions from previous operation. The Kocher maneuver is performed and the ligament of Treitz is mobilized. The proximal jejunum is passed behind the mesenteric vessels and divided with stapler. The duodenum is divided with stapler 2 centimeters below the pylorus. The gastroduodenal artery is dissected, ligated and divided between hemolocks. The common bile duct is divided with robotic scissors; however, the biliary stent is not found in the common bile duct. We suspected that it has migrated distally. Pancreas is divided with harmonic shears until identification of the pancreatic duct which is divided with scissors. Pancreatic head and uncinate process are carefully dissected from the portal vein and from the superior mesenteric artery. When the surgical specimen was only attached by a large branch from portal vein, this branch was dissected for hemolock insertion. However, hemolock insertion failed due to tissue resistance. We then realize that the missing biliary stent was, in fact, inside this portal branch and extended into the main portal vein. This branch is encircled and opened with identification of the biliary stent. Portal vein branch was clamped for safe removal of the biliary stent with minimum loss of blood. Reconstruction of the alimentary tract was then performed as usual. Surgical specimen is removed through extension of auxiliary port incision. Abdominal cavity is drained, and procedure is completed.

Results: Total operative time was 6 hours and 38 minutes. Estimated blood loss was 320 mL, with no need of transfusion. Recovery was uneventful and patient was discharged on the 7th postoperative day. Pathology confirmed ampulla of Vater adenocarcinoma T2N0M0. Patient is well with no signs of disease, 4 months after operation.

Conclusion: Robotic pancreaticoduodenectomy is safe and feasible even after ERCP complications that required laparotomy. Absence of endoprosthesis in the common bile duct may arise suspicion of wrongful insertion towards adjacent organs and must be dealt with caution.
Background: Hilar cholangiocarcinoma is considered as contraindication to the laparoscopic approach related mainly to the necessity of vascular dissection and a bilioenteric anastomosis. However with the development of minimally invasive pancreatoduodenectomy, we become more familiar with hepatic pedicle dissection, biliary anastomosis and even vascular resection-anastomosis. We present a video of laparoscopic left hepatectomy for hilar cholangiocarcinoma.

Methods: Hilar cholangiocarcinoma was discovered on jaundice in a 72 year old male and treated efficiently by endoscopic drainage. Lesion was located on the biliary confluence with left extension and no vascular invasion. The laparoscopic approach was decided and five trocars were used.

Results: The operative duration was 360 minutes; the blood loss was 200 ml, with isolated clampage of the portal vein of 30 minutes. The postoperative stay was marked by biliary fistula with spontaneous healing at POD 5 and the patient was discharged home at POD 14. Histology confirmed the diagnosis of a well differentiated cholangiocarcinoma of 3 cm with perineural invasion and no vascular invasion, 15 harvested negative lymph nodes and R0 resection (T2bN0R0).

Conclusion: The development and experience with laparoscopic pancreatoduodenectomy will increase the feasibility of some difficult liver resections by the laparoscopic approach including hilar cholangiocarcinoma.
V 14. LAPAROSCOPIC DISTAL PANCREATECTOMY AND SPLENECTOMY AFTER NEOADJUVANT CHEMOTHERAPY:
NEW DEMANDS IN COMPLEX PROCEDURES
ND Machado, F Kunzler, N Lad, R Jimenez, HJ Asbun
Presenter: Nuno Machado | Miami Cancer Institute

Background: Neoadjuvant therapy is being increasingly utilized in pancreatic ductal adenocarcinoma (PDAC) and significant responses to therapy have been observed. The feasibility and safety of the laparoscopic approach in this subgroup of patients is not yet established.

Methods: A 77-year-old man was diagnosed with borderline resectable PDAC. The tumor was 4 cm in size, located in the pancreatic neck and proximal body, encasing the origin of the splenic artery and with significant abutment of the celiac bifurcation along with the left lateral aspect of the common hepatic artery, and the head of the pancreas. Mild encasement and narrowing of the portosplenic confluence was also noted. The patient underwent 5 cycles of FOLFORINOX with minimal response. Hence, additional 5 cycles of Gemcitabine/Paclitaxel were administered to which he responded well. A significant tumor regression was noted. After 8 months of neoadjuvant chemotherapy, he underwent laparoscopic extended distal pancreatectomy with splenectomy.

Results: This video demonstrates the technical challenges and the need of significant expertise on these cases. It also illustrates the particular advantages of the magnification and exposure afforded by the laparoscopic approach, which result in a meticulous dissection to preserve the main vascular structures in a severely desmoplastic, post-neoadjuvant field.

Conclusion: Minimally invasive distal pancreatectomy is feasible in patients with locally advanced PDAC who demonstrate good response and tumor regression after neoadjuvant chemotherapy. Laparoscopically enhanced visualization is particularly important in these cases. There are different techniques and methods that can be used to overcome the challenges imposed by the post-neoadjuvant fibrosis and inflammation.
V 15. ROBOTIC RESECTION OF A TYPE IIIB KLATSKIN TUMOR
I Sucandy, S Ross, E Krill, M Castro, K Luberice, A Rosemurgy
Presenter: Iswanto Sucandy MD | Digestive Health Institute | AdventHealth Tampa

Background: This video depicts resection of hilar cholangiocarcinoma involving the biliary bifurcation, left and right hepatic bile ducts, undertaken in a 77-year-old woman. An 8mm trocar was placed through the umbilicus, and diagnostic laparoscopy was undertaken. Wedge liver biopsies of superficial lesions in segments V, VI, and VIII confirmed to be biliary hamartomas.

Methods: Portal dissection and lymphadenectomy was undertaken. The common hepatic artery, common bile duct, and the periportal lymph nodes were identified, excised, and sent to pathology for frozen sections. The bile duct was skeletonized down to the head of the pancreas. Utilizing the robotic monopolar scissor cautery, the distal common duct was transected, exposing the pre-existing biliary stents. The stents were removed. A 4-0 polypropylene suture was used to close the distal part of the common bile duct.

Results: Left total hepatic lobectomy was executed after examination of intrahepatic vasculature using the robotic ultrasound. The left hepatic artery and portal vein were isolated and transected. Traction sutures were placed on the left side of the liver transection line. The liver parenchymal transection was carried down toward the inferior vena cava using vessel sealer. The right hepatic duct was transected, and the final margin was confirmed to be negative for malignancy. The caudate lobe was mobilized off the inferior vena cava and included in the resection. A linear stapler was utilized to transect the left hepatic vein and the specimen was detached from the liver remnant. To begin the reconstruction, the ligament of Treitz was identified and the proximal jejunum was transected utilizing a robotic load stapler. A side-to-side stapled jejunojejunostomy was created. A 60cm Roux limb was constructed and transposed to the porta hepatis for the construction of the right Roux-en-Y hepaticojejunostomy. An end-to-side right-sided hepaticojejunostomy was completed utilizing the running V-Loc sutures. The anastomosis was buttressed with the omental flap. A JP drain was placed.

Conclusion: This video shows novel application of robotic platform for the type IV Klatskin tumor which are typically undertaken via open approach. The robotic system facilitates precise dissection and ease of suturing in bili reconstruction.
V 16. STANDARDIZED TECHNIQUE OF DISTAL PANCREATECTOMY WITH CELIAC AXIS RESECTION – TRICKS TO ACHIEVE ZERO MORTALITY OVER 53 CASES

Y Inoue, H Ito, A Oba, Y Ono, T Sato, Y Takahashi

Presenter: Yosuke Inoue  | Cancer Institute Hospital, Japanese Foundation for Cancer Research

**Background:** Distal pancreatectomy with celiac axis resection (DP-CAR) has been accepted as one promising option for advanced pancreatic body cancers. However, it contains difficulty in dissection of the celiac axis, risk of massive intraoperative bleeding, and potential risk of gastric ischemia due to defect of the left gastric artery, leading to high incidence of mortality.

**Methods:** In this video, we present the standardized technique of DP-CAR, by which we achieved no mortality over 53 cases. It includes 4 technical tips.

The first: Celiac first approach and clamping to minimize the blood loss during following dissection.

The second: Left kidney mobilization to obtain opened view during retroperitoneal dissection.

The third: Left gastric artery reconstruction to avoid ischemic gastropathy.

The last: Confirmation of blood flow of left gastric artery using ICG fluorescence imaging.

**Results:** Patients comprised 26 locally advanced, 17 borderline resectable, and 10 resectable according to NCCN guideline. UR-LA included 21 patients who underwent neoadjuvant therapy. Twenty-six patients underwent DP-CAR with high ligation of CA, and 27 underwent DP-CAR with CA ligation at distal of LGA origin (mDP-CAR). When compared between DP-CAR and mDP-CAR, operation duration (498 vs. 406 min, P=0.0018) was longer in DP-CAR and blood loss (664 vs. 520 ml, P=0.27) was similar among groups. Blood transfusion was needed in only one patient (2%) in DP-CAR group. Postoperative complication included ischemic gastropathy in 2, pancreatic fistula (B/C) in 18/1 (25%), and delayed gastric emptying in 15 (28%). Complication ≥ C-D grade 3 occurred in 17 patients (32%) without mortality. R0 resection was achieved in 21 (81%) vs. 24 patients (89%, P=0.47, 0mm rule).

**Conclusion:** DP-CAR is promising procedure to achieve R0 in advanced pancreatic body cancer. CA first approach, Left kidney mobilization, and LGA preservation/reconstruction are technical tips to minimize surgical risks.
Background: This video depicts a Roux-en-Y hepaticojejunostomy undertaken in a 43-year-old woman, who presented 5 days after a E4 bile duct injury during laparoscopic cholecystectomy for acute cholecystitis. Preoperative workup included a MRCP/MRI and triple phase CT scan confirming high bile duct injuries as well as right hepatic artery injuries.

Methods: An 8mm robotic port was placed at the umbilicus and diagnostic laparoscopy was undertaken. Clorpactin solution was used to wash out a significant amount of blood mixed with bile from the peritoneum. The injury occurred above the level of biliary bifurcation. An exploration of the bile duct, with a Fogarty catheter, was undertaken to confirm the anatomy of the biliary system. Findings showed active bile leak from both hepatic ducts. The extrahepatic biliary tree had been excised. The leaking hepatic ducts were prepared for anastomosis by placing 5-0 PDS sutures to join the left and right bile duct to a form of a new 8-shape biliary confluence.

Results: A mesenteric window was created at the proximal jejunum prior to transection with robotic stapler. 60 cm of Roux limb was constructed. Two enterotomies were made and a side-to-side jejunostomy was constructed utilizing a 45 blue load GIA robotic stapler. Then 3-0 V-Loc sutures were applied to close the common enterotomy. The posterior row of the hepaticojejunostomy was then completed right at the level of the hilar plate towards an opening in the jejunum utilizing a 6-inch V-Loc suture. A portion of segment 4B facing the porta hepatis was resected utilizing monopolar scissors and the bipolar energy device, to facilitate visualization to the area for the hepaticojejunostomy. The anterior row of the hepaticojejunostomy was then completed. A ‘watertight’ hepaticojejunostomy anastomosis was finalized with V-Loc sutures. Falciform and omental pedicle vascularized flaps were developed to buttress the hepaticojejunostomy posteriorly and anteriorly. A JP drain was placed.

Conclusion: This video documents a technically challenging biliary reconstruction involving a Strasberg E4 iatrogenic bile duct injury that was safely and efficaciously completed utilizing the robotic approach.
49. USE OF DEEP LEARNING TO PREDICT TUMOR RESPONSE TO NEOADJUVANT THERAPY IN PANCREATIC ADENOCARCINOMA: PURE AND HYBRID MODELLING

M Watson, M Baimas-George, K Murphy, R Pickens, D Iannitti, J Martinie, E Baker, D Vrochides, L Ocuin

Presenter: Michael Watson MD | Carolinas HealthCare System

Background: Neoadjuvant chemotherapy is being increasingly utilized for the treatment of pancreatic adenocarcinoma and is associated with improved survival. However, determining response to neoadjuvant therapy is difficult with preoperative imaging. New advances in artificial intelligence and deep learning techniques allow for novel analysis of images. Our hypothesis is that a deep learning model can be used to predict tumor response to neoadjuvant therapy.

Methods: We identified patients with pancreatic adenocarcinoma undergoing neoadjuvant therapy that underwent planned Whipple’s procedure between November 2009 and January 2018. Surgical pathology report was reviewed to determine tumor treatment effect, with grade 0-2 defined as treatment response and grade 3-4 defined as no treatment response. Only patients with adequate imaging and pathologically determined treatment effect were included for analysis. Computed tomography (CT) scans after neoadjuvant therapy and prior to surgery were reviewed. All axial slices of the tumor were obtained with 5mm spacing. These slices were converted to an image file for analysis. These images were used to create a deep learning model to predict tumor response to neoadjuvant therapy. Image augmentation using Gaussian blurring was used to increase the number of images for model creation and validation. Accuracy of the model was determined by area under the curve (AOC) and Brier statistics.

Results: 91 patients appropriate for image analysis (had appropriate CT imaging and tumor treatment effect documented by pathology report) were identified. Images were divided based on treatment response (333 images) or no treatment response (443 images) and image augmentation was used to artificially increase the image sample size. A “training set” of images consisting of 80% of patient images were used for creation of the deep learning model. Images from 73 patients were run through a 5-layer Convolutional Neural Network (CNN) with a flattened layer and two fully connected layers (LeNet model). Model initial training and validation accuracy were achieved to 100% with a loss function of < 0.02. The “testing” set of images consisted of images from 20% of patients. Images from the remaining 16 patients were then processed through the internally validated model. The model had an AOC of 0.7383 (p<0.001) and Brier statistic of 0.2347. Using the same procedure, a model was created with patients found to have greater than 10% reduction in CA 19-9 level after neoadjuvant chemotherapy (n=58). This improved the model with AOC improved to 0.7846 (p<0.0001) with Brier statistic of 0.1735.

Conclusion: A deep learning model can be used to predict response to neoadjuvant chemotherapy for patients with pancreatic adenocarcinoma. Model accuracy is further improved when combined with another indicator of tumor response (hybrid model). With further model improvement and increased patients for analysis, an application can be created to predict tumor response to neoadjuvant chemotherapy so as to safely obviate the need for subjective clinical interpretation.
50. THE ASSOCIATION BETWEEN BACTEROBILIA AND THE RISK OF POSTOPERATIVE COMPLICATIONS FOLLOWING PANCREATICODUODENECTOMY

M Parapini, JRA Skipworth, S Desai, S Chung, CH Scudamore, M Segedi, A Mah, PT Kim

Presenter: Marina Parapini MD | University of British Columbia

Background: Biliary bacterial colonisation (bacterobilia) is considered a risk factor for infectious complications after pancreaticoduodenectomy (PD). Intraoperative bile swabs taken during PD are frequently performed but interpreting and acting on the results remains unstandardized. The aim of this study was to investigate microbiota grown from PD biliary cultures in the context of pre-anesthetic antibiotic coverage and associated post-PD complications.

Methods: A retrospective study was conducted of 162 consecutive patients undergoing PD with biliary swab assessment between 2008 and 2018. Swab cultures were analyzed and sensitivities compared to pre-anesthetic antibiotics. Thirty day post-surgery infectious complications were assessed with regards to biliary culture growth, speciation of organism, and sensitivity to antibiotics.

Results: Bacterobilia was present in 136 patients (84.0%). There was a high incidence of multibacteria (100, 73.5%) with the most common organisms being Enterococcus (38, 27.9%), Streptococcus (21, 15.4%), and Klebsiella (19, 14.0%). There was a low incidence of Candida (15, 11.0%), vancomycin-resistant Enterococcus (VRE) (8, 5.9%), and extended spectrum beta-lactamase resistant bacteria (ESBL) (2, 1.5%). The majority of patients were administered cefazolin as pre-anesthetic antibiotic (146, 90.1%), either alone (135, 83.3%) or in combination with another antibiotic (11, 6.8%). Only 24 bile cultures grew bacteria sensitive to pre-operative antibiotics (17.6%).

Patients with bacterobilia (n=136) had significantly higher rates of major complications (Clavien-Dindo 3/4) than patients without bacterobilia (n=26) (33.1% vs 7.7%, p=0.017), as well as higher rates of surgical site infection/deep space infection (SSI/DSI) (56.9% vs 26.9%, p=0.010), and severe delayed gastric emptying (DGE) (DGE Grade C 28.9% vs 0%, p=0.031).

Upon comparison of patients with bile swabs demonstrating no growth (n=26), patients with bacterobilia sensitive to pre-operative antibiotics (n=24), and patients with bacterobilia not sensitive to pre-operative antibiotics (n=112), significantly lower rates of complications were seen in patients demonstrating no growth (major complications 7.7% vs 37.5% vs. 32.1% respectively, p=0.029) and SSI/DSI (26.9% vs 45.8% vs 58.9% respectively, p=0.011).

When individual bacterial species were assessed, Enterococcus was associated with higher rates of major complications (31.6% vs 7.7%, p=0.050), SSI/DSI (65.8% vs 26.9%, p=0.005), and organ space infection (OSI) (31.6% vs 7.7%, p=0.050). Streptococcus species were associated with a longer length of stay (15.0 median days vs 11.0, p=0.031), higher major complication rate (38.1% vs 7.7%, p=0.028), SSI/DSI rate (76.2% vs 26.9%, p=0.002), and ICU admission rate (19.0% vs 0%, p=0.034).

Conclusion: Positive biliary swabs taken at PD were associated with a higher incidence of major complications, SSI/DSI and severe DGE. Although there was a low incidence of fungal and multi-resistant organisms grown, pre-anesthetic antibiotic administration appeared to have no effect upon post-operative complications; however, the numbers assessed in this study are low and broadening of preoperative antibiotic coverage, particularly to include Enterococcus or Streptococcus species, should be considered. Patients with sterile bile cultures had the lowest risk of post-operative complications and efforts to reduce rates of bacterobilia, such as avoidance and limitation of biliary instrumentation, should similarly be considered.
<table>
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<th>Bacterobilia</th>
<th>Sensitive to Pre-Anesthetic Antibiotics</th>
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<th>Enterococcus</th>
<th>Streptococcus</th>
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<td>(Clavien-Dindo 3/4)</td>
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<tr>
<td>No</td>
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<td>8 (38.1%)</td>
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<td>59 (43.4%)</td>
<td>13 (54.2%)</td>
<td>46 (41.1%)</td>
<td>13 (34.2%)</td>
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<td>59 (43.4%)</td>
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<td>13 (34.2%)</td>
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<td>12 (31.6%)</td>
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<td>p=0.050</td>
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<td>6 (25.0%)</td>
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p=values derived from comparing to “no growth” biliary swabs
51. SPORADIC VS MEN-ASSOCIATED PANCREATIC NEUROENDOCRINE TUMORS: MULTI-INSTITUTIONAL CLINICOPATHOLOGIC COMPARISON

JR Bergquist, A Li, PD Worth, Q Ding, A Trickey, N Chatzizacharias, Z Soonawalla, P Athanasopoulos, C Toumpanakis, P Hansen, RW Parks, S Connor, K Parker, J Koea, S Srinavasa, B Ielpo, EV Lopez, B Lawrence, BC Visser

Presenter: John Bergquist MD | Stanford University

Background: Clinicopathologic distinctions of Multiple Endocrine Neoplasia (MEN) associated Pancreatic Neuroendocrine Tumor (PNET) are not well established. Prior studies have failed to define adequate criteria for surgical intervention in this patient group. Therefore, optimal surgical management remains unclear. We sought to improve knowledge of optimal surgical decision making in MEN-associated PNET.

Methods: We reviewed a multi-institutional international PNET database for patients who with MEN-associated or sporadic PNET. Cohort study design was used to compare clinicopathological characteristics between these two patient groups. Analysis of overall (OS) and disease-free survival (DFS) was performed. Propensity score matching was utilized to reduce bias between cohorts based on tumor size, t-stage, and age.

Results: The query identified 651 patients who met inclusion criteria (45 MEN1, 606 sporadic). Patients with MEN were diagnosed at a younger age (46 vs 58 years, p<0.01), and were more frequently of female gender (60.0 vs 49.4%, p<0.01). Patients with MEN were less likely to have a pancreatic head lesion (22.2% vs 36.7%, p<0.01), but more likely to have multifocal disease (71.1% vs. 18.6%, p<0.01). Lymph node involvement (28.9% vs. 30.7%, p=0.94), and the presence of metastasis (22.2% vs. 18.4% p=0.67) were not different between groups. MEN-associated tumors generally presented at a higher T-stage (75.6% vs. 54.8% stage 4, p=0.034). Although the type of procedure performed was similar between groups (22.2 vs. 27.6% pancreaticoduodenectomy, 42.2 vs. 44.6% distal pancreatectomy), the rate of total pancreatectomy was five times higher in the MEN cohort (15.6% vs. 3.3%, p=0.004). Median length of follow-up was 46 months. Survival analysis did not show significant differences between groups as median OS was not reached in the MEN cohort vs. 201 months in the sporadic PNET cohort. DFS was 126 months in the MEN cohort vs. 198 months in the sporadic cohort, but these curves were not statistically different (Figure). After matching was performed, survival remained similar between cohorts (OS median was not reached in either cohort, DFS 126 (MEN) vs 198 (Sporadic) months, p>0.5. Matched patients did not demonstrate differences in lymph node positivity rate (27.5 vs. 24.7%, p=0.913) or presence of metastatic disease (22.5 vs. 13.0%, p=0.29).

Conclusion: MEN-associated PNET occurs more frequently in younger, female patients, and is much more frequently associated with multi-focality and high t-stage. Survival for patients with MEN-associated PNET is excellent. Although MEN patients underwent total pancreatectomy at five times the rate of those with sporadic PNET, this may not be necessary in order to ensure long-term survival. Consideration should be given to active surveillance and/or parenchymal-sparing surgical interventions in order to preserve pancreatic function in this cohort of patients with indolent disease.
Overall Survival in PNET Patients

- Sporadic
- MEN

p = 0.011

Disease-Free Survival in PNET Patients

- Sporadic
- MEN

p = 0.785
52. PREDICTORS OF ENHANCED RECOVERY PROTOCOL DEVIATION IN PATIENTS UNDERGOING PANCREATODUODENECTOMY
T Daum, M Zenati, Al Al Abbas, K Smith, A Paniccia, J Holder-Murray, S Esper, M Boisen J Beane, A Zureikat
Presenter: Amr Al Abbas MD | University of Pittsburgh Medical Center

**Background:** Enhanced recovery protocols (ERP) are multi-modal, evidence-based protocols designed to reduce the stress response to surgery and facilitate faster recovery. Increasing evidence suggests ERPs can be used to reduce hospital length of stay (LOS) in patients undergoing a pancreateoduodenectomy (PD) without impacting complications and readmissions. However, a significant number of patients deviate from these pathways. Therefore, the aim of this study was to quantify and determine clinical factors associated with ERP deviation in patients undergoing PD.

**Methods:** A retrospective review of a prospective database of consecutive PDs performed under an institutional ERP (see table for an overview of ERP) from July 2015 to June 2018 was performed. ERP deviation was defined as development of any of the following clinically meaningful events: delayed gastric emptying (DGE as defined by the International Study Group for Pancreatic Surgery guidelines), need for patient-controlled analgesia (PCA), or prolonged LOS (highest quartile for LOS) during the index admission. Multivariate (MVA) logistic regression was used to identify predictors of deviation from ERP. Since complications can confound ERP outcomes, models were run with and without major (Clavien ≥3) complications as a variable. Analyses was performed on an intent to treat basis.

**Results:** A total of 410 patients (mean age 67, 47% female) underwent PD under an institutional ERP. Median LOS for the overall cohort was 7 days, and major (Clavien ≥3) complications occurred in 22%. Overall, 227 (55%) met the definition for ERP deviation. DGE occurred in 25%, PCA was utilized in 31%, and prolonged LOS (>9 days) was observed in 23%. On MVA of the entire cohort (inclusive of patients with major complications), intrathecal morphine (OR 0.47, CI 0.28-0.81, p=0.007) and pancreatic adenocarcinoma pathology (OR 0.57, CI 0.36-0.91, p=0.019) were protective against ERP deviation; whereas ketamine administration (OR 2.50, CI 1.10-5.70, p=0.028), pre-operative opioid use (OR 2.48, CI 1.38-4.45, p=0.002) and Clavien ≥3 complications (OR 4.15, CI 2.18-7.89, p=0.00) were associated with ERP deviation. After excluding patients with Clavien ≥3 complications, ERP deviation remained associated with ketamine administration (OR 3.83, CI 1.52-9.64, p=0.004), pre-operative opioid use (OR 2.77, CI 1.47-5.20, p=0.002), concomitant procedure (OR 2.10, CI 1.12-3.94, p=0.019) and prolonged post-operative pancreatic bed drain placement (OR 1.10, CI 1.03-1.17, p=0.005); whereas, intrathecal morphine (OR 0.44, CI 0.25-0.80, p=0.007) and a diagnosis of pancreatic cancer (OR 0.53, CI 0.30-0.92, p=0.025) remained protective against ERP deviation.

**Conclusion:** Deviation from ERP is common following a complex procedure such as pancreateoduodenectomy. This analysis identifies several patient, disease and treatment-related predictors of ERP deviation. Some of these modifiable factors can be leveraged to improve outcomes of pancreateoduodenectomy.
<table>
<thead>
<tr>
<th>Table 1. Brief overview of institution-specific ERP for pancreatoduodenectomy.</th>
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<tr>
<td><strong>Pre-operative patient education</strong></td>
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<tr>
<td>- Introduction to ERP: Discussion about diet and activity expectations.</td>
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<tr>
<td>- Nutrition counseling</td>
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<tr>
<td>- Pre-operative exercise and tobacco cessation encouragement</td>
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<tr>
<td><strong>Pre-operative preparation</strong></td>
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<tr>
<td>- No solid oral intake starting 2200 the evening before surgery</td>
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<tr>
<td>- Clear liquid diet allowed until 3 hours before surgery, emphasis on carbohydrate loading</td>
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<tr>
<td><strong>Pre-operative multi-modal anesthesia</strong></td>
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<tr>
<td>- 1000mg PO Acetaminophen</td>
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<tr>
<td>- 600mg PO Gabapentin (400mg if age ≥ 65 years)</td>
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<tr>
<td>- 400 mg PO Celecoxib (200 mg if age &gt; 65 years or renal insufficiency)</td>
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<tr>
<td><strong>Intra-operative Management</strong></td>
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<tr>
<td>- Intrathecal Morphine (100-200mcg, unless contraindicated) or Peripheral Nerve Block</td>
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<tr>
<td>- In setting of Peripheral Nerve Block: IV Ketamine infusion</td>
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<tr>
<td>- Prophylactic Antibiotic Administration</td>
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<tr>
<td>- Goal-directed fluid resuscitation</td>
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<tr>
<td>- Avoidance of IV opioids</td>
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<tr>
<td><strong>Immediate post-operative management</strong></td>
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<tr>
<td>- Remove Nasogastric tube</td>
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<tr>
<td>- Clear liquid diet</td>
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<tr>
<td>- Low volume IV fluids (40 mL/h)</td>
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<tr>
<td>- IV Acetaminophen</td>
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<tr>
<td>- PRN PO Oxycodone</td>
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<tr>
<td>- PRN IV Hydromorphone for breakthrough pain</td>
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<tr>
<td><strong>Post-operative day 1</strong></td>
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<tr>
<td>- Remove Foley catheter</td>
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<tr>
<td>- Clear liquid diet, Advance diet as tolerated</td>
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<tr>
<td>- Assess drain Amylase level (&lt;5,000 favorable)</td>
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<tr>
<td><strong>Post-operative day 3-4</strong></td>
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<tr>
<td>- Assess drain Amylase level (remove if Amylase level was &lt;5000 on POD1 and decreasing)</td>
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<tr>
<td>- Post gastrectomy, low residue diet</td>
</tr>
<tr>
<td><strong>Post-operative day 5-6</strong></td>
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<td>- Discharge</td>
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53. NEOADJUVANT CHEMOTHERAPY ALTERS THE BILIARY MICROBIOME IN PATIENTS WITH DUCTAL ADENOCARCINOMA UNDERGOING PANCREATICODUODENECTOMY

SO Nadeem, MR Jajja, DW Maxwell, SM Pouch, JM Sarmiento

Presenter: Syed Omair Nadeem MBBS | Emory University

**Background:** Postoperative infectious complications constitute a major source of morbidity in pancreatic surgery. For patients with pancreatic ductal adenocarcinoma (PDAC), the use of neoadjuvant chemotherapy is becoming more commonly adopted. Yet data is limited regarding its impact on the biliary microbiome. It has been hypothesized that the currently recommended peri-operative antibiotic coverages may be inadequate prophylaxis for patients undergoing pancreatic resection. The aim of this study was to determine the effect of neoadjuvant therapy on the biliary microbiome in patients with and without preoperative stenting as a surrogate for overall patient microbiome status.

**Methods:** Demographic, operative, post-operative, and biliary pathogen morphology and antibiotic sensitivity data was reviewed from consecutive patients with pathologically confirmed PDAC from January 2014 to December 2017. Data was expressed as percentages. Chi square and ANOVA testing was performed for comparison between groups.

**Results:** A total of 263 patients with PDAC were identified. 258 cases with complete stent data were included in the analysis. Of them 199 (77.1%) had received preoperative stenting, amongst whom 71 (35.7%) had received neoadjuvant chemotherapy. Ancef/Flagyl (n=167, 84%) was the most common antibiotic combination for perioperative prophylaxis followed by Clindamycin/Aztreonam (n=16, 8%). There were no significant differences in baseline characteristics between the people who did and did not receive neoadjuvant chemotherapy. The most common pathogens isolated from biliary cultures were Klebsiella Pneumoniae (n=31, 18.5%), Enterobacter Clocae (n=20, 11.9%) and E.Coli (n=16, 9.5%). Patients who did not receive neoadjuvant chemotherapy were more likely to grow fungi (5.5% vs 0% p=0.039), E.Coli and Enterobacter (25% vs 12.7%, p=0.039). However, growth of Gram-negative anaerobes (32.4% vs 18.8%, p=0.030) and unspecified bacterial species (31% compared to 14.8%, p=0.007) was higher in the patients who received neoadjuvant chemotherapy. Patients who did not receive neoadjuvant therapy were more likely to grow gram-negative pathogens resistant to Ampicillin-Sulbactam (47% vs 21%, p=0.007), Cefazolin (49% vs 28%, p=0.040), Cefotixin (42% vs 11%, p=0.009) and Cefuroxime (26% vs 4%, p=0.019) than the patients who did receive neoadjuvant chemotherapy. No differences were seen in resistance to Ampicillin (p=0.376), Aztreonam (p=0.977), Cefepime (p=0.172), Ceftriaxone (p=0.183) and Piperacillin-Tazobactam (p=0.36) (figure 1). Stratified by stent status, there were no differences in resistance patterns among patients who did and did not receive neoadjuvant chemotherapy.

**Conclusion:** Neoadjuvant chemotherapy significantly alters the biliary microbiome in patients with PDAC undergoing pancreaticoduodenectomy. Patients who did not receive neoadjuvant chemotherapy were more likely to grow pathogens resistant to cephalosporin antibiotics and have fungal colonization of their bile compared to patients who did receive neoadjuvant chemotherapy. Perioperative antibiotic coverage should be tailored to cover enterococci and gram negative organisms, especially for the subset of patients who had a biliary stent placed.
Figure 1: Resistance Patterns Amongst Gram Negative Organisms In Patients Who Were Stented

- PipTazo: 3% received neoadjuvant chemotherapy, 0% did not.
- Ceftriaxone: 3% received, 0% did not.
- Cefepime: 3% received, 0% did not.
- Cefazidime: 4% received, 2% did not.
- Aztreonam: 7% received, 6% did not.
- Cefuroxime: 4% received, 26% did not, p=0.019.
- Cefoxitin: 11% received, 42% did not, p=0.009.
- Ampicillin: 21% received, 47% did not, p=0.007.
- Cefazolin: 28% received, 49% did not, p=0.040.
- Ampicillin: 83% received, 87% did not.
54. CHANGE IN DRAIN AMYLASE IN THE EARLY POSTOPERATIVE PERIOD IS A BETTER PREDICTOR OF CR-POPF THAN USING POD 1 DRAIN AMYLASE ALONE

SB Ahmad, JC Hodges, A Bilderback, A Paniccia, DL Bartlett, AH Zureikat

Presenter: Sarwat Ahmad MD | University of Pittsburgh Medical Center

Background: Recent studies support early drain removal after pancreaticoduodenectomy (PD) in patients with a postoperative day (POD) 1 drain amylase (DFA1) level of < 5,000. However, several DFAs are frequently obtained beyond DFA1. The utility of those absolute values (DFA2) and change in DFA between DFA1 and DFA2 in predicting clinically relevant postoperative pancreatic fistula (CR-POPF) remains to be determined. We aimed to determine whether change in DFA is a more reliable predictor of CR-POPF compared to DFA1.

Methods: Using the ACS-NSQIP pancreatectomy database, PD patients from 2014-2017 with intraoperative drain placement, known DFA1, DFA2 (highest recorded value on POD 2-5), day of drain removal, and CR-POPF status (defined as fistula associated with percutaneous drainage ≥7 days or spontaneous wound drainage plus one major morbidity such as NPO-TPN, reoperation, organ/space SSI, unplanned intubation, ventilator, renal insufficiency, sepsis, or mortality) were retrospectively reviewed. Logistic regression models were used to estimate goodness-of-fit for DFA1, DFA2, and change in DFA as predictors of CR-POPF.

Results: 15,224 patients underwent PD with an 11.8% incidence of CR-POPF. Of the 2,778 patients who met inclusion criteria, CR-POPF rate was 6.6%. On multivariable risk adjustment, DFA1 plus change in DFA was compared to DFA1 or DFA2 alone in its ability to predict the risk of CR-POPF. Risk of CR-POPF increased with any rise in DFA (for example: 20% increased odds for a 50% rise in DFA; 40% increased odds for a 100% rise, p<0.001), regardless of whether the DFA1 was above or below 5,000. Risk of CR-POPF significantly decreased with any drop in DFA for a maximum odds reduction of approximately 50% with a 75% or more decrease in DFA (p=0.979). Notably, the degree of odds reduction was not associated with the starting DFA1 value (p=0.979). While DFA, DFA2, and DFA1 plus change in DFA were all independent predictors of the risk of CR-POPF (all p<0.001 after multivariable risk adjustment), DFA1 plus change in DFA performed better than either DFA1 or DFA2 alone (Pseudo R2 = 0.294 vs 0.262 and 0.287, respectively), with a 98.1% negative predictive value for CR-POPF.

Conclusion: CR-POPF after PD is more accurately predicted by DFA1 plus change in DFA rather than DFA1 alone, and can decrease by 50% with a 75% drop in DFA. These data should be used together with the DFA1 to select patients for early drain removal. Future directions include validating a nomogram for using these variables to guide drain management following PD.
Risk of CR-POPF decreases with reduction in DFA, independent of DFA1

Risk of CR-POPF (%) vs % Drop in DFA from POD 1 to POD 2-5

p<0.001*
55. VALIDATING BIOLOGIC AGE TO PREDICT SURVIVAL IN OLDER PANCREATIC CANCER PATIENTS
Presenter: Anthony Scholer MD, MBS | John Wayne Cancer Institute at Providence St. John Health Center

Background: Frailty based on biologic age using a deficit-accumulation principle (DAFI) can characterize a decline in health more efficiently than chronological age. Therefore, the objective of this study was to calculate a DAFI score and its association with survival in pancreatic cancer.

Methods: The SEER-MHOS linked databases were retrospectively reviewed from 1998-2017 to identify all patients >65 years of age without any cancer history, as well as a cohort with pancreatic cancer (PC) that completed a MHOS survey within one year of PC diagnosis. A 25-variable mean DAFI score (mDAFI) (using activities of daily living, chronic health conditions, functionality, general and mental health statuses as variables) was constructed from 2,054,808 unique non-cancer patients. The validity of the DAFI to determine a PC patient’s biologic age was examined through its relationship with chronological age. Linear regression calculated the predicted DAFI score (pDAFI) based on chronologic age and cutoff values for PC frailty were constructed, with frailty defined as mDAFI (of PC patients) > pDAFI (of non-cancer) by age. Differences in mDAFI by age and sex in PC patients, as well as the association of mDAFI with overall survival (OS) was analyzed.

Results: In non-cancer patients, mDAFI was almost completely correlated with chronological age (r^2=0.98; p<.001) whereas in PC patients, mDAFI was somewhat less correlated with chronological age (r^2=0.77; p<.001). Of 242 PC patients, 61% were considered frail. Although the frailty rate was similar across all ages, the mDAFI score increased with age in both males and females (P=0.01), but without statistical difference by sex. The median OS for PC was 10.05 months (CI: 7.82-12.09), with a median follow-up of 10.1 months. Frail PC patients had a significantly decreased median OS (7.13 months, CI: 5.65-10.1) compared to non-frail PC patients (16.08 months, CI: 11.47-34.4) (p=0.001). Frail PC patients also had a significantly decreased 1-year (frail: 37%, non-frail: 55%, p<0.001), 3-year (frail: 18%, non-frail: 38%, p<0.001), and 5-year (frail: 14%, non-frail: 27%, p<0.001) OS. After controlling for other factors, both increasing age (aHR:1.03, CI: 1.01-1.06) and increased frailty (aHR:1.53, CI: 1.16-2.00) were significantly associated with a decreased OS in PC patients; gender and race had no impact on OS. In addition, each 10% increase in DAFI score was associated with an 18% increased risk of death (aHR:1.18; CI: 1.07-1.30, p<0.001).

Conclusion: In this older PC cohort, frailty using a DAFI retained a significant negative association with OS after controlling for age, emphasizing the difference between chronological and biologic age and the impact of frailty on OS. Further research should explore the utilization of DAFI to construct personalized treatment plans for older PC patients.
56. REGIONAL LYMPHADENECTOMY IN HEPATOMA RESECTION: INSIGHT INTO PROGNOSIS

JR Bergquist, A Li, MM Dua, BC Visser
Presenter: John Bergquist MD | Stanford University

Background: Recent developments in chemotherapeutics for hepatocellular carcinoma (HCC) suggest that new trials of adjuvant therapy are on the horizon. Selection criteria for these trials are as yet undetermined, but prior experience with intrahepatic cholangiocarcinoma suggests that surgical determination of lymph node status may be relevant. To date, the importance of regional lymphadenectomy for prognostication after resection of HCC is poorly understood. We sought to ameliorate this knowledge gap through a nationwide population-based analysis.

Methods: Patients with HCC who underwent liver resection (LR) were identified from the Surveillance Epidemiology and End Results (SEER-18) database (2003-2015). Patients undergoing transplant were excluded. A cohort-based study design was used to make clinicopathologic comparisons between patients grouped based on completion of regional lymphadenectomy, defined as removal of any lymph nodes. Propensity-score matching based on age, tumor size, t-stage, and fibrosis score was utilized to reduce bias. Unadjusted and adjusted analysis of overall (OS) and disease-specific survival (DSS) were performed.

Results: 5395 patients were included, of which 835 (15.4%) had regional lymphadenectomy completed. While distribution of race, gender, and fibrosis score were similar between cohorts, patients who got regional lymphadenectomy had larger tumors (7.0 vs 4.8 cm), and higher t-stage (30.9 vs. 17.6% T3+ - all p<0.001). Among patients who underwent lymphadenectomy, the overall node positivity rate was 12.0%. Patients who underwent negative lymphadenectomy had equivalent median OS as patients who did not undergo lymphadenectomy (50 months in both cohorts) while DSS was similar (28 months vs. 29 months). Patients found to have node positive disease had substantially decreased OS (20 months) and DSS (16 months, both log-rank p<0.01). The matching algorithm was performed with two controls per case and produced balance among matched covariates (all p>0.1). In the matched cohort, patients undergoing lymphadenectomy had equivalent unadjusted OS (46 vs. 43 months, log-rank p=0.869) and DSS (27 vs 29 months, log-rank p=0.306) to those who did not undergo lymphadenectomy. The prognostic impact of node positive disease persisted in the matched cohort (OS 24 months, DSS 19 months, both log-rank p<0.01). Adjusted overall mortality hazard was independently elevated in patients found to have N1 disease (1.71 unmatched, 1.56 matched, both p<0.01). Disease-specific mortality hazard was independently elevated at 1.40 (p<0.01 prior to matching), but not independently elevated at 1.25 (p=0.09 after matching).

Conclusion: Regional lymphadenectomy is performed in only approximately 15% of patients undergoing surgery with curative intent for HCC. Regional lymphadenectomy provides useful prognostic information which can guide patient selection for adjuvant chemotherapy, as well as better facilitate multidisciplinary management of HCC. The prognostic value of regional lymphadenectomy is persistent when adjusted for T-stage. As the era of adjuvant therapy for HCC begins, surgeons should increasingly consider performing regional lymphadenectomy to facilitate optimal multidisciplinary management.
57. RENIN-ANGIOTENSIN INHIBITION AFTER PARTIAL HEPATECTOMY REDUCES TUMOUR GROWTH AND MODULATES TUMOUR IMMUNITY
GE Riddiough, T Fifis, K Walsh, V Muralidharan, MV Perini, C Christophi
Presenter: Marcos Perini MD, MS, PhD | University of Melbourne

**Background:** Experimental and clinical data demonstrates that liver regeneration after hepatectomy drives tumour progression in the residual liver. Previously, we have shown that renin-angiotensin inhibitors (RASi) attenuate growth of colorectal liver metastasis (CRLM) in the non-regenerating liver. The aim of this study is to assess the efficacy of RASi at reducing CRLM growth within the microenvironment of the regenerating liver following partial hepatectomy.

**Methods:** Male CBA mice underwent induction of colorectal liver metastases (CRLM) in conjunction with 70% partial hepactectomy. They were treated with either control or RAS inhibitor, captopril 250mg/kg via intraperitoneal injection. Formalin fixed tissues were used for immunohistochemistry and fresh tissues for flow cytometrical analysis of myeloid derived suppressor cell and T cell subsets. In vitro, mouse colorectal cancer cell lines were treated with serum from mice following 70% hepatectomy, sham surgery or under standard cell culture conditions.

**Results:** In vitro, serum obtained after liver resection stimulated significantly greater cellular proliferation than serum from controls and standard culture conditions (p <0.0001). In the regenerating liver RASi significantly reduced tumour burden (p<0.01). RASi was also associated with a two-fold reduction in the number of PDL1 positive macrophages (p=0.58) and a reduction in the intensity of PDL1 expression. RASi was also associated with a significant upregulation of both CD4 and CD8 T cells (p=0.01 and p=0.01 respectively), as well as a two-fold increase in the percentage of double negative T cells (p<0.01). Moreover, RASi induced a change in the phenotype of CD8 and double negative T cells by significantly increasing their expression of PD1 (p=0.01 and p<0.01 respectively).

**Conclusion:** Liver regeneration after hepatectomy drives tumour progression and this is attenuated by RASi. RASi are immunomodulatory and re-direct the immune response in favour of immune destruction of tumour cells. RASi reduce both the number of PDL1 positive macrophages and the density of PDL1 expression on macrophages and also induces immunomodulatory effects on T cells within the microenvironment of the regenerating liver.
58. ANALYSIS OF THE NATURAL COURSE OF PEDIATRIC PORTAL HYPERTENSION
Presenter: Al-Faraaz Kassam MD | Cincinnati Children’s Hospital Medical Center

Background: The etiology of portal hypertension (pHTN) in children varies from that of adults and requires understanding of the differences in management strategies. We set out to assess the epidemiology and natural history of pediatric pHTN.

Methods: 154 patients with pHTN from 2008-2018 were identified at a free-standing children’s hospital. Etiology, disease course, and interventions were assessed. Patients were then stratified by etiology of pHTN. The primary outcome was overall survival, with a secondary outcome of understanding the interventions and management required. Survival was calculated using Kaplan-Meier survival analysis. Statistical significance was set at p<0.05.

Results: The distribution of etiology included 105 (68%) patients with cholestatic disease (CD), 16 (10%) with fibrotic or hepatocellular disease (HFD), four (3%) with hepatic vein obstruction (HVO), and 29 (19%) with pre-hepatic pHTN (PRE) caused by portal vein obstruction or portal vein sclerosis. Median follow-up for the cohort was 4.63 (IQR 2.02-7.25) years. Median age at diagnosis (years) varied between etiologies (0.34, IQR 0.06-0.9 CD vs 0.51, 0.06-3.33 HFD vs 5.85, 1.26-9.52 HVO vs 2.51, 0.85-5.09 PRE; p<0.01). There were no differences in sex, comorbidities, or years of follow up. Patients with PRE were more likely to require an EGD (79.3% vs 40% CD, 50% HFD, 50% HVO, p<0.01) and patients with PRE (2.0±0.4) and HVO (1.8±1.0) required more endoscopic interventions than CD (1.1±0.2) or HFD (1.4±0.5) (p<0.01). However, there were no differences regarding gastrointestinal bleeding or need for banding or sclerotherapy (p=0.31 and p=0.94 respectively). Interventions differed based on etiology (p<0.01) with CD more likely undergoing a transplant only (71.4%) and PRE more likely to undergo a shunt only (44.8%). 24.8% of CD, 62.5% of HFD, 100% of HVO, and 41.4% of PRE patients did not undergo an intervention. Kaplan-Meier analysis revealed no difference in survival based on etiology, however, analysis by type of intervention revealed a significant increase in mortality in the group who received no intervention compared to shunt, transplant, or both (p<0.01) (Figure 1). Of the 18 patients who died without intervention, 7 patients died while listed for transplant, five patients were not candidates due to progression of disease, and six patients had clinical deterioration before workup was completed. Of the 36 patients who are alive and have not undergone intervention, 27 have stable pHTN, six are waitlisted for organs, and three are not candidates for intervention due to severity of disease.

Conclusion: The sequelae of pHTN in children is distinct from the adult process and a better understanding of this disease is necessary. In this single institution study, we found that most patients presented with CD as the cause of pHTN followed by PVO. While no difference in overall survival was noted between groups, patients who received no intervention had higher mortality than those who received an intervention. Early referral to specialized centers with experience managing these complex disease processes may allow for improved risk stratification and early intervention which may improve outcomes. Further work is needed to understand the predictors of mortality in patients with pHTN.
59. DIGITAL 3-DIMENSIONAL LIVER MODEL AIDS IN SURGICAL PLANNING FOR LIVER TUMORS
ME Czerwonko, K Labadie, K Sullivan, JO Park
Presenter: Matias Czerwonko MD | University of Washington

Background: Accurate interpretation of anatomy is crucial for preoperative planning, and it relies heavily on the surgeon’s ability to mentally reconstruct 2-dimensional (2D) axial radiologic images into 3D constructs. This is especially the case in liver surgery, and given the complex surgical anatomy of the liver, this mental exercise can be challenging for surgical trainees. The objective of this study is to determine whether a 3D model of preoperative axial imaging improves the surgical trainee’s assessment of liver lesions and aids in surgical planning.

Methods: High-quality, multiphase, liver-protocol computerized tomographic (CT) scans of patients with hepatic tumors were obtained and reconstructed into 3D PDF models accessible using Adobe Acrobat Reader. A questionnaire was administered to surgical residents at a single institution to assess interpretation of surgical anatomy, query a proposed surgical plan and evaluate residents’ perceived confidence in their answers. Residents completed the questionnaire twice, initially with CT scan only and then again with the CT scan and 3D model accessible. Participants had 4 minutes per case to complete the questionnaire.

Results: 32 surgical trainees participated in the study. Access to the 3D model resulted in a higher percentage of correct answers on objective questionnaire versus CT scan only (49% vs 76% correct, p<0.0001). The improvement was observed in both junior residents (PGY 1-2; 42 vs 70%, p<0.001) and senior residents (PGY 3-5; 60% vs 83%, p=0.003). Overall percent correct increased in 10 of 11 questions when 3D model was accessible. 72% of participants reported higher degree of confidence in answers when the 3D model was accessible versus using the CT alone. All participants reported the 3D model to be helpful overall in interpretation of each patient case. 97% of participants reported it assisted in identifying the tumor’s relationship with nearby structures, 85% reported assistance in identifying number of tumors present, 63% with the location of the tumors, and 50% reported it helpful with surgical planning.

Conclusion: 3D modeling of liver anatomy is a helpful tool to facilitate accurate anatomic interpretation and surgical planning for surgical trainees. The usefulness appears to be present regardless of the level of training, background knowledge or recent HPB experience. 3D models improve confidence in assessing anatomy and resectability of liver lesions, empowering the surgical trainee to increase participation in patient care.
PLATELETS SPECIFICALLY ACCUMULATE AT THE SITE OF LIVER REGENERATION AND STIMULATE INTERLEUKINE-6 PRODUCTION IN SINUSOIDAL ENDOTHELIAL CELLS

D Pereyra, R Baumgartner, S Holzer, S Haegele, C Brostjan, T Grünberger, P Starlinger

Presenter: Patrick Starlinger MD | Mayo Clinic, Rochester

Background: Interleukin-6 (IL-6) is a well-known regulator of liver regeneration, specifically during the early period. Similarly, platelets have been identified to affect liver regeneration significantly in rodent models as well as humans. Within this project, we wanted to identify the time course of IL-6 production within the human liver during the early phase of liver regeneration as a result of the potential interaction of platelets and liver sinusoidal endothelial cells (LSECs) and determine their effects on postoperative outcome.

Methods: Liver tissue was collected prior and 2 hour after induction of liver regeneration in patients undergoing liver resection. Electron microscopy was used to determine the behavior of platelets in the liver sinusoids shortly after induction of liver regeneration. IL-6 mRNA was analyzed in liver tissue at the same time point. Further, IL-6 serum levels were evaluated perioperatively.

Results: Platelets were shown to adhere to LSECs and even translocated in the space of Disse early after induction of liver regeneration. Circulating IL-6 levels significantly increased after liver resection. Within liver tissue we observed a significant induction of IL-6 expression (mean: 13 fold). Intriguingly, while circulating IL-6 levels were not associated with clinical outcome, patients developing postoperative liver dysfunction (LD) displayed a significantly higher induction of IL-6 (LD: 25 fold, no LD 9.3 fold, P=0.001) already two hours after induction of liver regeneration. Ultimately, IL-6 induction by platelets was also observed in co-culture experiments with LSECs.

Conclusion: Platelets adhere to LSECs early after induction of liver regeneration in humans and might be a critical trigger for induction of IL-6 expression. This initial burst of IL-6 might be crucial for induction of liver regeneration. Nevertheless, an overshooting IL-6 production seems not to be beneficial for patients undergoing liver resection but seems to result in an overwhelming inflammatory response that ultimately leads to liver dysfunction.
61. DETECTION OF TUMOR MULTIFOCALITY IN RESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA: DEFINING THE OPTIMAL PRE-OPERATIVE IMAGING MODALITY


Presenter: Thomas Sutton MD | Oregon Health and Science University

**Background:** Tumor multifocality (TM) in intrahepatic cholangiocarcinoma (ICC) is a known negative prognostic factor, and its presence is often a contraindication to hepatic resection. Lack of standardized pre-operative liver imaging practices may contribute to undiagnosed multifocality and poor outcomes with an increased risk of intrahepatic recurrence. We sought to investigate the sensitivity of cross-sectional imaging modalities to detect TM in ICC treated at a multidisciplinary hepato-pancreato-biliary cancer program within an NCI Comprehensive Cancer Center.

**Methods:** We identified n=52 patients with ICC who underwent curative resection from 2004-2017. The timing and modality of pre-operative imaging was recorded, and the findings compared with pathologic outcomes. The Time from Imaging to Surgery (TIS) was defined as the time interval in days between the last imaging study prior to the operation and the hepatic resection to include: liver-protocol magnetic resonance imaging (MRI), multiphasic contrast computed tomography (CT), and positron emission tomography (PET).

**Results:** Overall, prior to hepatic resection, 41 (79%) patients had a CT, 17 (33%) patients had an MRI, and 30 patients (57%) had a PET at any time during their pre-operative staging evaluation. The abdominal imaging modality serving as the last pre-operative staging scan was CT in 58% (n=30), followed by PET (n=13, 25%) and MRI (n=9, 17%). The median TIS was 20 days (SD 19 days, range 1-87 days). TM was identified pre-operatively in 5 patients (10%) with an additional 4 patients discovered to have TM on final pathology—an 80% increase. Of the 4 patients found to have undiagnosed TM on pre-operative imaging, the median TIS was 20 days (SD 5.4 days, range 13-26) and none had undergone MRI. Two of the 4 patients (50%) with intra-operatively discovered TM had non-alcoholic fatty liver disease (NAFLD). The overall sensitivity and specificity of MRI in detecting TM pre-operatively was 100% in our population.

**Conclusion:** CT and PET are inadequate for the accurate pre-operative diagnosis of TM in patients with resectable ICC with detection of only half of multifocal cancers, even if performed within 30 days of resection. Contrast-enhanced liver MRI should be considered the standard pre-operative imaging staging modality in all patients with ICC undergoing hepatic resection, especially for patients with NAFLD.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>52</td>
</tr>
<tr>
<td>Age, years; median (IQR)</td>
<td>64 (55-70)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (50%)</td>
</tr>
</tbody>
</table>

**Underlying Liver Disease**
- Chronic viral hepatitis: 4 (8%)
- NAFLD: 24 (46%)
- NASH: 12 (23%)
- Cirrhosis: 3 (6%)
- None: 12 (23%)

**Imaging Characteristics**
- Last pre-operative abdominal staging modality
  - Multiphasic CT: 30 (58%)
  - PET: 13 (25%)
  - Liver protocol MRI: 9 (17%)
- Time from imaging to surgery, days; median (IQR): 20 (12-42)
- Pre-operatively identified TM (>1 liver segment): 5 (10%)
- Pre-operatively identified satellitosis (within 1 liver segment): 1 (2%)

**Tumor Characteristics on Final Pathology**
- Largest tumor size, centimeters; median (IQR): 5.5 (2.9-7.5)
- Tumors with multifocality or satellitosis: 13 (25%)
- Multifocal tumors (>1 liver segment): 9 (17%)
  - Pre-operatively diagnosed TM: 5 (56%)
  - Undiagnosed TM: 4 (44%)
  - Overdiagnosed TM: 0 (0%)
- Satellitosis (within 1 liver segment): 4 (8%)
  - Pre-operatively diagnosed satellitosis: 1 (25%)
  - Undiagnosed satellitosis: 3 (75%)
  - Overdiagnosed satellitosis: 0 (0%)

Abbreviations: IQR=Interquartile Range; NAFLD=Non-Alcoholic Fatty Liver Disease; NASH=Non-Alcoholic Steatohepatitis; CT=Computed Tomography; PET=Positron Emission Tomography; MRI=Magnetic Resonance Imaging; TM=Tumor Multifocality
62. LIVER MOLDING WITH ALPPS DOES NOT DELAY: THE DIFFERENCE IN RIOT AFTER TRISECTIONECTOMY

M Baimas-George, RC Pickens, M Watson, J Sulzer, KJ Murphy, L Ocuin, E Baker, JB Martinie, DA Iannitti, D Vrochides

Presenter: Maria Baimas-George MD, MPH | Carolinas HealthCare System

Background: Resection of primary and secondary liver tumors with trisectionectomy may necessitate liver molding techniques for adequate future liver remnant (FLR) to avoid post-operative liver failure. The complications and delays of surgery, however, can impact a patient’s return to intended oncologic therapy (RIOT). Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) has been shown to stimulate a more rapid FLR regeneration in comparison with the traditional technique of portal vein embolization (PVE). This study evaluated whether a difference in RIOT exists with or without liver molding and between liver molding techniques (ALPPS and PVE) with trisectionectomy.

Methods: A retrospective review evaluated trisectionectomies for malignancy from 2008-2018 in a single tertiary institution. Clinical and oncologic outcomes were compared between cases with and without liver molding (ALPPS or PVE). The chemotherapy-free interval (CFI) for RIOT was determined for patients who received neoadjuvant and planned adjuvant chemotherapy, including those who died prior to receiving intended treatment. CFI was calculated in two ways; 1) time from first surgery to first adjuvant chemotherapy treatment; and 2) time from first surgery to clinical clearance to initiate chemotherapy treatments.

Results: Fifty-one patients underwent trisectionectomy of which 11 patients underwent ALPPS, 14 underwent PVE, and 26 did not require any liver molding technique. Of these patients, 73% of ALPPS patients, 64% of PVE patients, and 58% of patients without liver molding achieved RIOT and there was no statistical difference between groups in this ability to achieve RIOT (p = 0.6951). The RIOT groups were compared and there were no statistical differences found in age, gender, race, type of malignancy, R0 resection rate, length of stay, readmission rate, post-operative complication or 90-day mortality. CFI to first adjuvant chemotherapy treatment was significantly different between the 3 groups (ALPPS: 3.3 months; PVE: 5.2 months; None: 2.4 months, p = 0.0203). CFI to clearance for adjuvant chemotherapy was also significantly different between groups (ALPPS: 2.2 months; PVE: 3.2 months; None: 2.0 months, p = 0.0268).

Conclusion: The necessitation of liver molding for extended liver resections should not cause undue apprehension towards a patient’s return to adjuvant chemotherapy as there is no difference in the ability to achieve RIOT with liver molding. The type of liver molding technique, however, should be considered as there is a significantly shorter RIOT in ALPPS versus PVE.
<table>
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<tr>
<th>Characteristic</th>
<th>ALPPS (n = 8)</th>
<th>PVE (n = 9)</th>
<th>No Liver Molding (n = 15)</th>
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<td>Robotic</td>
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<tr>
<td>Open</td>
<td>5 (63)</td>
<td>8 (89)</td>
<td>14 (93)</td>
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<td>R0 Resection</td>
<td>6 (75)</td>
<td>7 (78)</td>
<td>11 (73)</td>
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<td>Length of stay (days)</td>
<td>9.9 (4.6)</td>
<td>8.8 (7.8)</td>
<td>10.1 (9.5)</td>
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</tr>
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<td>4 (27)</td>
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<td>Grade II</td>
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<td>Grade V</td>
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<td>Time to RIOT (months)</td>
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<td>353 (111)</td>
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<td>3 (33)</td>
<td>7 (47)</td>
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<td>Time to recurrence (days)</td>
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<td>365 (104)</td>
<td>357 (196)</td>
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<td>&lt;90 Day Mortality</td>
<td>1 (13)</td>
<td>1 (11)</td>
<td>2 (13)</td>
<td>1.000(=)</td>
</tr>
</tbody>
</table>

Data reported as n-value (%) or median (stdev)
63. PERIOPERATIVE MORTALITY AFTER LIVER TRANSPLANTATION CAN BE PREDICTED AT THE TIME OF LISTING
M Molinari, S Dharmayan, D Jorgensen
Presenter: Michele Molinari MD, MSc | University of Pittsburgh Medical Center

Background: Best clinical judgment is currently used to estimate the likelihood that a patient referred for a liver transplant (LT) will survive after the operation. The primary aim of this study was to assess if perioperative risks (<24 hours) could be stratified using the liver transplant risk score (LTRS), a prognostic model previously developed to estimate the risk of postoperative mortality based on recipients’ preoperative characteristics. Secondary aims were to assess if the model could also stratify the risk of 30-day, 1-year mortality and patient survival beyond the first year.

Methods: The LTRS was calculated using parameters available when patients were listed for LT: MELD score, BMI, Age, Diabetes, and Renal Failure (defined as the need for dialysis). Mortality rates at 24 hours, 30 days, and 1-year were compared among group of patients with different LTRS. Patients with ABO-incompatible LT, redo, multivisceral, partial graft and malignancies except for hepatocellular carcinoma were excluded. The demographic and preoperative clinical characteristics of 18,635 adults who had a LT in the United States between 2013 and 2017 were extracted from the Scientific Registry of Transplant Recipients.

Results: For the entire cohort, 24-hour, 30-day and 1-year mortality rates were 0.9%, 2.6%, and 8.2% respectively. 24-hour mortality was 0.6%, 0.7%, 1.0%, 1.2%, 1.3%, 1.7% for patients with LTRS equal to 0, 1, 2, 3, 4 and >5, respectively (P for trend <0.001). 30-day mortality was 1.6%, 2.4%, 3.1%, 3.2%, 3.9% and 5.5% respectively (P for trend <0.001). 1-year mortality was 5.5%, 7.7%, 9.9%, 9.3%, 10.8%, and 15.4% respectively (P for trend <0.001) (Figure 1). For low-risk patients (0-1 points), mortality rates at 24-hour, 30-day and 1-year were reduced by 24%, 25% and 20% respectively (P<0.001). For intermediate-risk patients (2-3 points), mortality rates at 24-hour, 30-day and 1-year were 23%, 20% and 18% higher than expected (P<0.001). For high-risk patients (>4 points), the standardized mortality ratios at 24-hour, 30-day and at 1-year were respectively 60%, 71% and 51% higher than expected (P<0.001). The overall 4-year survival of the entire cohort was 84%. For patients with 0, 1, 2, 3, 4, and >5 points, 4-year survival was 82%, 79%, 78%, 82%, 78%, and 66% respectively (P for trend <0.001). For low-risk recipients, 4-year survival was higher than expected (84% vs. 82%) while the opposite was found for high-risk recipients (76% vs. 82%) (P<0.001).

Conclusion: 24-hour, 30-day and 1-year mortality after LT can be estimated preoperatively using the LTRS. The LTRS could also predict long-term patient survival. The findings of this study suggest that the LTRS could reduce inter-observer variability for the identification of patients at increased risk of poor outcomes after LT.
Postoperative Mortality

Percentage

- 24-hours mortality
- 30-day mortality
- 1-year mortality
64. THE VIABILITY OF LIVER TRANSPLANTATION IN PATIENTS AGE 70 AND OLDER: AN UPDATED REVIEW
K Mahendraraj, I Kim, K Kosari, G Voidonikolas, T Todo, T Brennan, A Klein, N Nissen
Presenter: Krishnaraj Mahendraraj MD | Cedars-Sinai Medical Center

**Background:** Liver transplantation in the elderly has been regarded with caution due to lower survival and increased morbidity. In this study, postoperative outcomes of orthotopic liver transplantation (OLT) in patients age 70 and older are compared to younger cohorts to assess its safety and efficacy.

**Methods:** Data on 55,267 OLT recipients were abstracted from the Scientific Registry of Transplant Recipients (SRTR) over a 10 year period (2007-2017). Three age-based subgroups were created: elderly (age 70 and over), middle-age (age 50-69), and young (age 18-49). Pediatric recipients (age < 18) were excluded. Standard statistical analysis was performed using donor and recipient data to compare indications, mortality and graft survival.

**Results:** There were 1,622 elderly OLT patients (2.9%), compared to 40,271 middle-age patients (72.9%) and 13,374 young patients (24.2%). Significantly fewer elderly patients had a BMI>30 compared to other groups (26.6% vs. 37.2% and 33.4%, p<0.01). The median MELD-Na score of elderly patients was significantly lower (18.4 vs. 21.6 and 27.2, p<0.01), with 63.8% elderly patients being MELD < 20. Most elderly patients received OLT for hepatocellular carcinoma (HCC)-exception status (665 patients; 41%). Fewer elderly patients were Status 1. They had a significantly lower pretransplant INR and bilirubin, and higher albumin. Elderly patients spend a significantly longer time on the waitlist, and tended to receive organs from older age donors. Elderly patients received organs from donors with higher rates of diabetes, hypertension, history of malignancy and macrosteatosis. Elderly patients also received a higher proportion of DCD and ECD organs. Elderly patients had lower overall survival (66.15% vs. 71.4% and 71.7%) and lower graft survival (68.4% vs. 73.9% and 75.7%), p<0.01. There were more graft complications observed in the elderly including hepatic artery thrombosis, infection, primary non-function, primary graft failure and vascular thrombosis, but these were not statistically significant. Elderly patients had a significantly lower 6-month (6.9%) and 1-year (8.7%) rejection rate compared to other groups (12% and 14%, respectively). Kaplan-Meier survival analysis of 5-year graft survival was 3.98 years in the elderly compared to 4.03 years in middle-age and 4.76 years in young recipients, p<0.001. There was no significant difference between survival estimates of elderly patients with HCC vs. non-HCC.

**Conclusion:** Elderly OLT recipients tended to be in a better state of health at the time of transplant, and tended to wait longer for donor organs with more marginal characteristics. Despite having a significantly lower overall and graft survival rate, this difference (less than 5%) was not clinically significant. These results suggest that OLT is a safe and viable treatment for the elderly, even when using marginal donor organs.
<table>
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<tr>
<th>Variable</th>
<th>Disease</th>
<th>Logistic Regression</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
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<td>60-69</td>
<td>1.23 (0.97-1.57)</td>
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<tr>
<td></td>
<td>≥70</td>
<td>1.85 (1.42-2.40)</td>
<td>0.0005</td>
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<tr>
<td></td>
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<td>1.04 (0.80-1.36)</td>
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<tr>
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<td>1.02 (0.84-1.25)</td>
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<td>1.07 (0.84-1.37)</td>
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<td>0.98 (0.77-1.26)</td>
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<tr>
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<td>1.26 (1.03-1.55)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Donor Source</td>
<td>Living</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Deceased</td>
<td>0.97 (0.81-1.17)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Table 1. Demographics and Clinical Parameters for 55,267 Orthotopic Liver Transplantation Recipients from the Scientific Registry of Transplant Recipients (SRTR) Database (2007-2017)
Background: While the International Normalized Ratio (INR) was developed to standardize administration and titration of warfarin in patients needing anticoagulation, it is now also used as a general indicator of bleeding diathesis. Patients undergoing liver surgery can have abnormally elevated INR and may have venous thromboembolism prophylaxis withheld as a result. To support optimal venous thromboembolism (VTE) screening and prophylaxis practices, we examined the association between pre-operative INR elevation and VTE events following hepatectomy.

Methods: Hepatectomies captured in the American College of Surgeons National Surgical Quality Improvement Program registry between 2007 and 2016 were included. INR was treated as a categorical variable (categories: 0.9-1.1 [reference], 1.1-1.2, 1.2-1.4, and 1.4-2.0). Patients with identified bleeding disorders or INR >2.0 were excluded to avoid analyzing the effect of bleeding diathesis or anticoagulation. Patients with missing INR values were compared with those with recorded values in terms of baseline characteristics. Univariable and multivariable main effect models were developed to examine the effect of elevated preoperative INR on 30-day postoperative VTE (deep venous thrombosis or pulmonary embolism), major bleeding (transfusion and unplanned return to operating room), major morbidity, and mortality, adjusting for potential patient-level and clinical confounders.

Results: We included 29,867 elective hepatectomies (63.4% partial lobectomies, 9.9% left hepatectomies, 18.0% right hepatectomies, 8.6% trisegmentectomies). The median age of the patients was 60 years old (interquartile range 50-68 years) and 48.2% were female. Pre-operative INR was reported in 25,789 patients (86.3%) and there were no significant differences in baseline characteristics between patients with missing and recorded INR. INR was elevated in 3,089 patients (12.2%): 1.1-1.2 in 8.1%, 1.2-1.4 in 3.3%, and 1.4-2.0 in 0.9%. Incremental elevations in INR from 0.9-1.1, to 1.1-1.2, to 1.2-1.4, to 1.4-2.0 presented increasing rates of 30-day postoperative VTE (2.6% vs 3.5% vs 4.8% vs 4%, p<0.001), major bleeding (1.6% vs 2.3% vs 4.2% vs 5.4%, p<0.001), major morbidity (29.7% vs 40.0% vs 52.2% vs 52.0%, p<0.001), and mortality (1.4% vs 3.1% vs 5.9% vs 8.0%, p<0.001). Incremental elevations in pre-operative INR were independently associated with higher risk of VTE, major bleeding, major morbidity, and mortality, after adjusting for age, sex, cancer diagnosis, race, ASA classification, pre-operative hemoglobin, pre-operative platelet level, and extent of liver resection.

Conclusion: An elevated preoperative INR was counter-intuitively associated with increased risk of both VTE and major bleeding following hepatectomy. The role of peri-operative management in this association warrants further investigation to determine optimal care in the presence of elevated pre-operative INR to improve patient outcomes.
66. OUTCOMES FOLLOWING SYNCHRONOUS RESECTION OF COLORECTAL CANCER PRIMARY AND LIVER METASTASES

MR Driedger, T Szabo Yamashita, N Machairas, KL Mathis, SP Cleary, DM Nagorney

Presenter: Michael Driedger MD | Mayo Clinic, Rochester

Background: Colorectal cancer (CRC) is third most common cancer diagnosis in both males and females in North America. It is estimated that over 50% of patients will develop CRC liver metastases (CRCLM), while 20% of patients will have metastatic disease present at the time of diagnosis. Simultaneous resection of synchronous colorectal liver metastases is optimal in the appropriate clinical setting.

Methods: Consecutive cases of synchronous resection of both the CRC primary and CRCLM were reviewed retrospectively at a single, high-volume institution over a 17-year period (2000-2017). Two-way statistical analyses were used to compare categories. Analysis of survival was performed using Cox regression model. Statistical significance was defined as p<0.05.

Results: 273 patients underwent simultaneous resection of CRCLM. The distribution of the primary lesion was similar between the colon (52.4%) and rectum (47.6%), while 46.9% of patients had bilobar liver disease. In total, 62.6% of patients received neoadjuvant chemotherapy. A mean of 3.4 liver lesions were resected. The majority of patients (81.7%) underwent subsegmentectomy/wedge resection during the procedure demonstrating a preference for non-anatomic parenchymal sparing technique. Hemihepatectomy was performed in 24.1%, while 24.9% underwent segmentectomy/sectionectomy and 15.8% received intraoperative ablative therapy. An R0 hepatic resection rate of 94.9% was achieved. Total morbidity rate was 51.2%, with colorectal and liver specific morbidity occurring in 23.8% and 9.2% of patients. Specifically, the anastomotic leak rate was 2.2%, while post hepatectomy liver failure occurred in 1 patient (0.4%). Inpatient re-operative intervention was required in 6.6% of patients, while 30- and 90-day mortality rates were 1.1% and 4.0% respectively. In individuals who underwent combined major liver (hemihepatectomy, trisectionectomy) and major colorectal (left colorectal resection with diversion, abdomino-perineal resection, subtotal colectomy) resections (n=24), total morbidity and liver specific morbidity were similar at 62.4% (p=0.291) and 20.8% (p=0.069) respectively. Colorectal specific morbidity and inpatient re-operative intervention were increased at 50.0% (p=0.005) and 20.8% (p=0.012) respectively. Mortality at 30- and 90-days was similar (4.2%, p=0.994). In the modern (2013-2018) cohort of patients (n=86), 83.7% received neoadjuvant chemotherapy with a mean of 6.3 cycles, of which FOLFOX was most commonly employed. Adjuvant therapy was delivered in 84.9% with a mean time interval of 7.2 weeks. In this cohort, median survival was not reached while estimated 5-year survival was 67.6%. Postoperative complications delayed the planned administration of chemotherapy in 17.8% (mean time to therapy of 11.1 weeks) and precluded adjuvant therapy in just 3.5%. Delay in chemotherapy administration did not influence survival (hazard ratio (HR) for death 0.88, 95% confidence interval (CI) 0.26-4.92, p=0.88) while failure to receive adjuvant chemotherapy, because of patient decision or post-operative complication, was associated with significantly worsened survival (HR for death 0.18, 95% CI 0.049-0.68, p=0.011).

Conclusion: Concurrent resection of both the primary colorectal lesion and CRCLM is preferred in the appropriate clinical setting and necessitates an individualized therapeutic strategy. A perioperative chemotherapeutic approach is associated with excellent 5-year survival, while postoperative complications precluding the delivery of adjuvant systemic therapy decrease survival.
67. COMBINATION IRREVERSIBLE ELECTROPORATION AND IMMUNOTHERAPY FOR LOCAL AND ABSCOPAL CONTROL OF MULTIFOCAL HEPATIC TUMORS

C O'Neill, Y Li, Y Yu, S Li, W Guo, R Martin

Presenter: Conor O’Neill MD | University of Louisville School of Medicine

Background: Among patients with advanced hepatocellular carcinoma (HCC), outcomes remain poor. Sorafenib, an oral kinase inhibitor, remains the standard therapy but provides only marginal survival gains with a 10.7-month median overall survival. Recently, data have shown that combination ipilimumab, a CTLA-4 inhibitor, and nivolumab, a programmed cell death protein-1 inhibitor, provide objective response rates observed in 31% of patients and a disease control rate approaching 50%. Non-thermal tumor disruptive therapies are also of interest for advanced HCC for their ability to induce cell death without coagulative necrosis. This provides a theoretical advantage by increasing tumor antigen release for immune recognition and response. Irreversible electroporation (IRE) can be utilized around critical structures for non-thermal destruction of tumors. IRE has also been postulated to have an abscopal effect on lesions not in the tumor-ablative field, possibly through heightened immunologic response. We evaluated whether combination nivolumab (+) ipilimumab and IRE would lead to increased tumor necrosis and T cell recruitment to both the treated tumors and tumors outside the local ablative field.

Methods: C57L/J mice (Jackson Laboratory, ME) underwent laparotomy and tumor implantation of 1mm^3 sections of Hepa1-6 tumors into the right and left lobes of the liver. Tumors were allowed to mature for 2 weeks. Five groups of mice (n=30) were measured: Group 1 mice were controls with no tumor, Group 2 mice had tumor implantation alone, Group 3 received IRE with 2500 Volts at a pulse length of 100us, pulse interval 100ms and 10 pulses to the left lobe tumor, Group 4 received weekly intraperitoneal injections of ipilimumab (3mg/kg) and nivolumab (10 mg/kg) for 4 weeks and Group 5 received IRE and combination immunotherapy for four weeks. After treatment, the liver was harvested for analysis. Co-culture cell-migration studies were performed. Briefly, hepa1-6 cell cultures either alone or following IRE-treatment were plated into 24-well plates in serum-free medium or medium containing ipilimumab and nivolumab. Co-culture insets were placed in each well containing 1X10^5 mouse lymphoma T cells. Cell migration was analyzed by cell counting at six hours.

Results: Mouse tumors treated with IRE (Groups 3&5) had extensive necrosis visible on H&E staining (figure 1). Group 4 mice treated with immunotherapy alone demonstrated minimal tumor necrosis or peritumoral infiltrate. There were significant increases in both tumor necrosis and CD-8(+) T-cell infiltrate for tumors outside the electroporated field for mice treated with both immunotherapy and IRE (p<0.05); tumors treated with IRE directly and immunotherapy had significantly greater necrosis and peritumoral CD-8(+) T cell infiltrate than tumors outside the treated field or for tumors in Groups 1-4 (p<0.05). Similarly, cell migration studies confirmed significantly higher T cell recruitment in cultures containing electroporated Hepa1-6 cells and combination immunotherapies.

Conclusion: Murine models of hepatocellular carcinoma demonstrate significant increases in peritumoral T cell recruitment and tumoral necrosis of both primary and abscopal tumors when IRE and combination immunotherapy are utilized. Further research is required to develop mechanistic insight prior to clinical trial initiation.
68. UTILIZATION OF THE KAWAGUCHI-GAYET COMPLEXITY CLASSIFICATION TO STRATIFY HEPATECTOMY PATIENTS FOR DISTINCT ENHANCED RECOVERY PATHWAYS BASED ON ANTICIPATED LENGTH OF STAY

BJ Kim, C Gaskill, TE Newhook, E Arvide, WL Dewhurst, HS Tran Cao, YS Chun, TA Aloia, JN Vauthey, CD Tzeng

Presenter: Bradford Kim MD | The University of Texas MD Anderson Cancer Center

Background: The Kawaguchi-Gayet (K-G) Classification of laparoscopic hepatectomy complexity was recently validated for open liver resection, making it potentially useful for preoperatively stratifying patients into distinct postoperative pathways based on anticipated length of stay. The objective of this study was to use the K-G classification to stratify patients based on anticipated length of stay for the creation of distinct enhanced recovery pathways.

Methods: A single-institution prospectively maintained (data entry by advanced practice providers and biweekly review by faculty) hepatectomy database was queried to identify a continuous set of patients from 1/1/2017-12/31/2018. There was no universal enhanced recovery protocol stratifying surgical extent that was uniformly applied during this time. The previously described 3-level K-G classification was utilized for open operations: Grades I (“low” complexity, or non-anatomic resection for anterolateral or posterosuperior segment and left lateral sectionectomy), II (“intermediate,” or anterolateral segmentectomy and left hepatectomy), and III (“high,” or posterosuperior segmentectomy, right posterior sectionectomy, right hepatectomy, central hepatectomy, and extended hepatectomy). All minimally invasive (MIS) hepatectomies were separately categorized, and hepatectomies performed in conjunction with another procedure (e.g. hernia repair or bowel resection) were labeled as “Combo.” All hepatectomies were classified into one of four categories: MIS, Low-Intermediate Complexity (K-G I-II), High Complexity (K-G III), and Combo. Standard statistical analyses were conducted to compare patient demographics, clinical outcomes, perioperative variables, and length of stay (LOS) among the hepatectomy classifications.

Results: Of 466 patients (median age 57 years [interquartile range, IQR, 40-66 years]; 54% male), the distribution of hepatectomies included: 86 (18.5%) MIS, 168 (36%) Low-Intermediate Complexity, 140 (30%) High Complexity, and 72 (15.5%) Combo. Median operative time correlated with increasing complexity (MIS: 163, Low-Intermediate: 251, High: 338, Combo: 385 minutes, p<0.001). Major complications (Modified Accordion Grade ≥3) occurred more frequently with more complex (K-G Class III) hepatectomies (MIS: 3 [4%), Low/Intermediate: 17 [10%], High: 25 [18%], and Combo: 9 [13%], p<0.001). The median LOS for the entire cohort was 4 days (IQR 3-6 days). Median LOS was associated with approach and difficulty (MIS: 2 IQR 1-3, Low: 4 IQR 3-5, High: 5 IQR 4-6 and Combo: 5 IQR 4-7 days, p<0.001, Figure 1). Univariate analyses identified longer operative time, the surgical drain, regional analgesia (regional nerve block vs. epidural) and complexity of operation to be associated with prolonged LOS (LOS > median 4 days). Subsequent multivariate analysis confirmed that K-G classification (Low/Intermediate: OR 5.5, High: OR 11.6, Combo: OR 11.8, p<0.001) was the greatest predictor of LOS.

Conclusion: Kawaguchi-Gayet Classification grouped a contemporary cohort of patients undergoing hepatectomy into four strata with LOS durations of 2-5 days, allowing improvements to be applied to individual pathways rather than across very different complexity levels with disparate outcomes. Simply using surgical approach and K-G Classification, all future patients can be grouped into four pathways at the time of surgical consent, allowing providers and patients to discuss length of stay expectations a priori in clinic.
Figure 1. Length of stay and rates of major complications between complexity of hepatectomy
69. THE ROLE OF THE Na/K-ATP-α1-CAV-1/SMAC/SURVIVIN PATHWAY IN NASH RELATED HCC GENESIS

U Udoh, A Malick, G Smith, P Kumar, JD Sanabria, Schade M, JA Sanabria, K Sodhi, S Pierre, Z Xie, J Shapiro
Presenter: Juan Sanabria MD, MSc | Case Western Reserve & Marshall University

Background: The incidence of Hepatocellular Carcinoma (HCC) and its related mortality is increasing in the world, as it is the 3rd cause of cancer related mortality, USA (7th cause) and the Appalachian population (2nd cause), mainly from the metabolic cellular disturbances promoted by the epidemic of obesity and a paucity of markers for its early detection. Our group has shown that in addition to the regulatory signaling for cell metabolism, the α1-subunit of the Na/K-ATPase (NKA) interacts with the anchoring protein caveolin-1 to provide a pathway for organogenesis during cell development. In addition, it may promote suppression of tumor development through SMAC/Survivin involvement. Furthermore, blockage of such a path, by pNaKtide inhibited cell replication of tumor cell lines. We propose uncoupled metabolism acts in tandem with an unbalanced NKA α1-caveolin-1/SMAC/Survivin circuit enhancing cell immortality.

Methods: Quantitation of the expression of caveolin-1, SMAC-Diablo and Survivin proteins was performed by confocal microscopy on immuno-stained livers from subjects with normal livers (n=10), patients with NASH (n=20), patients with cirrhosis and HCC from NASH (n=11) and patients with liver metastases (n=12). Plasma levels of referred proteins were measured by ELISA. Significant differences among groups were established at p<0.05 using ANOVA/t-test.

Results: Protein expression in liver tissue among groups are displayed in Figure 1. The expression of caveolin-1 and Survivin are significantly higher in liver tissue from patients with NASH/HCC when compared to normal livers or livers with mets. In contrast, SMAC-Diablo protein expression is significantly lower in liver tissue with NASH or HCC. Similar trends were observed in plasma levels of described proteins (p<0.05).

Conclusion: The expression and plasma concentration of caveolin-1, SMAC-Diablo and Survivin proteins differed significantly in patients with NASH related cirrhosis±HCC when compared to normal livers or livers with metastases. Inhibition of this path could lead to disease prevention or even disease regression. Furthermore, protein markers may serve as markers for early tumor detection in high risk populations.

![Graphs showing protein expression in liver tissue and plasma levels of caveolin-1, SMAC-Diablo, and Survivin](image-url)
**Background:** Pancreatic ductal adenocarcinoma (PDAC) continues to be one of the leading causes of cancer death in the Unites States, with an increasing incidence over the past decades. Despite the high mortality rate and dismal prognosis, the therapeutic responses are poor and heterogenous even to our current standards of treatment. Recently it has been shown that PDAC could be subdivided into clinically relevant subgroups using immunohistochemistry (IHC) for two protein markers, KRT81 and HNF1A. We aimed to validate their IHC-subtyping and evaluate the gene expression HNF1A and KRT81 in an upfront-resected PDAC cohort. Alternative PDAC subtyping using gene-expression profiles have been previously described by Collisson and Bailey, which we aim to see their overlap using our cohort.

**Methods:** We performed IHC for HNF1A and KRT81 on 61 patients with upfront resected PDAC from 2010 to 2014. These were read by a board-certify pathologist confirming its presence or absence in the tumor cells. Of the 68 patients, 34 patients had RNAseq. Gene expression analysis for KRT81/HNF1A were generated, from which gene expression ratio were calculated. Expression of HNF1A/KRT81 in the The-Cancer-Genome-Atlas (TCGA) pancreatic cancer database, were similarly evaluated on 138 patients after the data was obtained from cBioPortal. Using RNAseq as a more sensitive test, the accuracy, sensitivity, and specificity of IHC-subtyping was accessed. Molecular subtyping was also performed as previously described by Collisson and Bailey.

**Results:** Using IHC-subtyping, we were able to validate the results of the previous study. The IHC HNF1A-subtype showed a better overall and disease-free survival than KRT81. Similarly, the HNF1A positive RNAseq subtype had a statistically better overall survival and disease-free survival over the KRT81 positive subtype (P < .016 and P < 0.023, respectively). When validated externally using the TCGA-database, the RNAseq HNF1A subtype had a statistically better disease-free survival than the KRT81 subtype (P < 0.0193). We were not able to recapitulate this on the overall survival given the early censorship of the TCGA cohort of patients. Using gene expression as a more sensitive tool, the accuracy (53%), sensitivity (54%) and specificity (75%) were calculated. Thus, IHC had a better positive than negative predictive value (84% vs 6%) in stratifying PDAC. Additionally, our gene profile subtypes did not match the previously described subtypes of Collisson and Bailey as they did not correlate with survival outcomes in our patients.

**Conclusion:** RNAseq stratification was able to accurately recapitulate the IHC subtypes of PDAC using the gene expression of HNF1A and KRT81, which was associated with significant different outcomes in both our internal cohort of upfront resected PDAC and externally using the TCGA database. Unfortunately, we were not able to recapitulate the previous molecular subtyping defined by Collisson and Bailey. This study, introduces a more sensitive analytical tool, RNAseq, for the stratification of this PDAC subtypes, which may play a role in our future understanding of the biology of these two subgroups. With the growing development in price and workflow, RNAseq analysis on endosonographically acquired core needle biopsies may serve as a biomarker-based stratification stool for PDAC patients.
Figure 1. Exemplary images of IHC staining in an HNF1A nuclear positive tumor in figure 1a. Exemplary images of IHC staining of a KRT 81 cytoplasmic positive tumor. Kaplan-Meier curves of disease-free survival of RNAseq-derived subtypes of PDAC in the TCGA database, figure 1c. P values calculated by log-rank test. Ticks denotes censored cases. Kaplan-Meier curves of overall survival of RNAseq-derived subtypes of PDAC in our upfront resected cohort in figure 1d.
71. LONGITUDINAL ISLET FUNCTION AND INSULIN REQUIREMENT AFTER TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION
W Lancaster, S Owczarski, D Adams, K Morgan
Presenter: William Lancaster MD | Medical University of South Carolina

Background: Total pancreatectomy with islet autotransplantation is treatment for chronic pancreatitis. Though a significant proportion of patients do not require insulin postoperatively, evidence suggests that insulin independence declines over time. The objective of this study is to measure long term islet function and insulin independence after TPIAT.

Methods: A retrospective analysis of a prospectively maintained database of patients undergoing TPIAT was conducted. Postoperative islet function was measured with serum C peptide levels. Postoperative insulin requirements and hemoglobin A1C values were tabulated.

Results: A total of 190 patients were included. The mean islet transplant dose was 3545 IEq/kg. The mean serum C-peptide level was constant at 1.1 ng/mL at 6 months, 1 year, and 2 years postoperative. This decreased significantly to 0.5 ng/mL (p<0.05) at 3 years postoperative and remained at this level at 5 years postoperative. The rate of insulin independence was 32% and 30% at 1 and 2 years postoperative, respectively. Insulin independence declined at 3 years postoperative to 23% (p<0.05) and 20% at 5 years postoperative. The mean insulin requirement (units/day) was 26, 25, and 28 at 1, 3, and 5 years postoperative, respectively. Mean postoperative hemoglobin A1C values at 1, 3, and 5 years postoperative were 8.0, 8.2, and 7.8.

Conclusion: Islet function declines over time after TPIAT with a corresponding decline in insulin independence rates at 3 years postoperative. In spite of this, glycemic control remains stable. Further study is needed to understand the decline in islet function over time and to develop preventive strategies.
**72. ACCURACY OF NODAL STAGING AND MANAGEMENT OF EXTRA-HEPATIC CHOLANGIOCARCINOMA**  
*P Blinn, T Maramara, J Huston, P Briceno, R Shridhar*  
**Presenter:** Ken Meredith MD | Florida State University, Sarasota Memorial Hospital

**Background:** Extra-hepatic cholangiocarcinomas (EHC) are low-incidence cancers that are difficult to diagnose and associated with a dismal prognosis. Surgery remains the only option to improve survival. We sought to examine the accuracy of clinical nodal staging for extra-hepatic cholangiocarcinoma and evaluate outcomes with surgery and adjuvant therapies.

**Methods:** Utilizing the National Cancer Database we identified patients who underwent resection for EHC. We then stratified by T stage, N stage (clinical (C), pathologic (P) and adjuvant therapy (chemo(AC) or chemoradiation(CRT). Baseline comparisons of patient characteristics were made using Mann-Whitney U, Kruskal Wallis and Pearson’s Chi-square test as appropriate. Survival analyses were performed using the Kaplan-Meier method. Multivariable cox proportional hazard models (MVA) were developed to identify predictors of survival. All statistical tests were two-sided and p <0.05 was considered significant.

**Results:** We identified 3106 patients diagnosed with EHC and a median age of 68 (20-90) years. There were 1976 (63.6%) males and 1130 (36.4%) females, p<0.001. The median tumor size was 2.2 cm (1.5-3) and 1562 (50.5%) were node positive. Of those undergoing portal lymphadenectomy (PL), the median nodes removed was 11 (5-19) and mean nodes positive were 1.5 ± 2.6. R0 resections were performed in 2269 (73.1%). Adjuvant therapy was administered in 1627 (52.4%) of patients (AC =722 (23.2%), CRT=905 (29.2%). Of those whose clinical node status was N0, 37.3% were pN+. Those patients whose nodal status was unknown cNX, 59.6% were pN+. Patients with cN+ subsequently were pN+ 95.6%. Median and 5 year survival for those pN0 vs pN+ patients was 41.7 mo and 37% vs 25 mo and 23%, p<0.001. Adjuvant therapy improved overall and 5 year survival compared to those who did not receive subsequent therapy (none= 31.5 mo and 30% vs AC 28.9 mo and 24% vs CRT 34.8 mo and 33%), p=0.02. There was no benefit seen in node negative patients, p=0.14. However in node positive patients median and 5 year survival was benefited by AC and CRT (none= 21.3 mo and 21% vs AC 25 mo and 19% vs CRT 27.8 mo and 27%), p=0.002. Additionally, portal lymphadenectomy substantially improved median and 5 year survival (no PL=23.2 mo and 29% vs PL=43.1 mo and 37%), p=0.003.

**Conclusion:** Clinical accuracy of nodal staging for extra-hepatic cholangiocarcinoma remains dismal. Surgery to include portal lymphadenectomy significantly improves survival. Adjuvant therapy improves survival in node positive patients, and in patients with R1 resections.
73. CACHEXIA AND CHOLANGIOCARCINOMA: IMPLICATIONS ON PROGNOSIS AND IMMUNOMODULATION

Li Ruffolo, N Ullman, A Melucci, S Qin, P Juvilier, R Kaur, A Chacon, R Jewell, M Georger, DC Linehan, PA Prieto

Presenter: Katherine Jackson MD | University of Rochester

Background: Cachexia is a hallmark of advanced stage cancers, and has been repeatedly associated with poor prognosis and worse overall outcomes across malignancies. Patients with cholangiocarcinoma (CCA) often present with weight loss, but the incidence of sarcopenia and its effect on late stage CCA patient survival remains undescribed. Recent studies investigating mice with cancer associated cachexia showed metabolic derangements and downstream suppression of immune function. Here we present our experience with a spontaneous murine model of CCA and real time monitoring of muscle mass to investigate cachexia and its implications on the maintenance of an immunosuppressive tumor microenvironment.

Methods: A retrospective review of patients with unresectable CCA was performed. Cross sectional imaging acquired on disease presentation was reviewed, and the cross sectional area of the psoas muscle at the third lumbar vertebra was measured and normalized by height to obtain the skeletal muscle index (SMI). Lab values such as serum albumin levels at time of diagnosis were recorded. Survival curves were analyzed. Human CCA tumors underwent immunohistochemistry staining. Mice with targeted KRAS activation and loss of p53 (KPPC) were weighed and monitored with high frequency ultrasound twice weekly for development of hepatic tumors and for development of sarcopenia as defined by a 12% decrease in right thigh muscle diameter. Tissue acquired from mouse CCA tumors and littermate control livers were processed for histology, immunohistochemistry, RNA sequencing, mass cytometry, and RT-PCR.

Results: Patients with lowest quartile SMI had significantly shorter survival from disease onset than those with middle/highest quartile SMI (p<0.01), with a mean survival of 136 and 283 days, respectively [Figure 1A]. Patients with low serum albumin also had worse overall survival (p<0.01) [Figure 1B]. Human tumors exhibited marked immunosuppressive features on immunohistochemistry. KPPC mice reliably developed hepatic tumors as well as sarcopenia. Notably, the KPPC mice more often demonstrated weight gain rather than weight loss as their disease progressed secondary to large tumor burden and ascites. CCA tumors of mice with end stage disease revealed increased expression of checkpoint markers and soluble factors indicative of increased immunosuppression, as well as known drivers of cachexia. Functional metabolic markers assessed by RNA sequencing were significantly altered in murine tumor samples vs. normal liver.

Conclusion: Sarcopenia is evident in patients presenting with unresectable CCA, and is associated with worse overall survival. CCA in the spontaneous mouse model reliably induces a cachectic state as evidenced by both sarcopenia and metabolic derangement, despite the absence of weight loss, and recapitulates the highly immunosuppressive tumor microenvironment seen in human disease. Using this robust model and real time in vivo monitoring of muscle mass, agents targeting cancer associated cachexia can be reliably tested in the spontaneous model.
Figure 1: Survival curves of patients with A) low and high skeletal muscle index (SMI) and B) low and normal serum albumin. Patients with sarcopenia as defined by lowest quartile SMI had significantly shorter survival from disease onset (136 vs. 283 days) ($p<0.01$). Low albumin (albumin <3.2) was also significantly associated with shorter survival ($p<0.001$).
74. TOTAL NEOADJUVANT THERAPY FOR RESECTABLE AND BORDERLINE RESECTABLE PANCREATIC CANCER
R Kim, K Christians, M Aldakkak, C Clarke, B George, P Ritch, M Kamgar, N Kulkarni, A Khan, W Hall, B Erickson, D Evans, S Tsai
Presenter: Rebecca Kim MD, MPH | Medical College of Wisconsin

Background: Neoadjuvant therapy (NT) prior to surgical resection is the standard of care for borderline-resectable (BLR) pancreatic cancer (PC). There is also general consensus that overall survival is optimized with a total of approximately six months of nonsurgical therapy (chemotherapy +/- radiation therapy). However, there is no consensus on the sequencing of therapies and most investigators have sandwiched surgery between pre- and post-operative systemic therapy. Due to the risk of not completing the postoperative portion of the treatment program, total neoadjuvant therapy (TNT), or surgery-last, is gaining popularity. In this study, we examine the use of TNT in the treatment of patients with resectable and BLR PC.

Methods: An institutional prospective pancreatic cancer database was retrospectively reviewed for consecutive patients treated with neoadjuvant therapy for resectable and BLR PC between 2009 and 2019. TNT was defined as a minimum of 16 weeks of chemotherapy, and radiation or chemoradiation therapy. Patients were dichotomized into those who received TNT and those who received a shorter course of neoadjuvant therapy. Patients were excluded if they did not receive any neoadjuvant therapy. Demographic, clinical, and pathologic variables were examined, including Charlson comorbidity index and CA19-9 levels during treatment. Outcomes of interest included rates for proceeding to surgical resection and overall survival.

Results: In total 415 patients were included in the study, 171 (41%) patients had resectable disease, and 244 (59%) had BLR PC. The median age was 66 (range [37, 89]) years, and 202 (49%) patients were female. TNT was administered to 72 (17%) patients. A shorter duration of NT was administered to 343 (83%). TNT was administered to 31 (18%) of 171 patients with resectable PC and 41 (17%) of 244 patients with BLR PC. Of the 393 patients with available preoperative CA19-9, 32 (47%) of 68 patients in the TNT group and 170 (52%) of 325 patients in the shorter NT group normalized their CA19-9 level (p =0.43). Twelve (17%) of the 72 patients in the TNT group did not proceed with surgical resection due to disease progression. This was not statistically different from the NT group (p=0.34). The type of surgical procedure and need for vascular reconstruction did not differ between the two groups. The median overall-survival (OS) was the same for both, (25.1 vs 24.8 months, p=0.6).

Conclusion: As systemic therapies continue to improve, the rationale for TNT will become even more compelling as it ensures the delivery of all intended systemic therapy to all operated patients. This study suggests that patients who can tolerate shorter NT can probably tolerate a bit more (TNT) as evidenced by similar rates of surgical resection in those who received TNT compared to a sandwiched approach. TNT for resectable and BLR PC will likely become the backbone of future clinical trials involving patients with operable PC.
PATHOLOGIC COMPLETE RESPONSE FOLLOWING NEOADJUVANT THERAPY FOR PANCREATIC DUCTAL ADENOCARCINOMA: DEFINING THE INCIDENCE, PREDICTORS, AND OUTCOMES

J Cloyd, C Shen, M Dillhoff, A Manilchuk, A Ejaz, T Pawlik, A Tsung
Presenter: Jordan Cloyd MD | The Ohio State University

Background: Neoadjuvant therapy (NT) is increasingly utilized for patients with pancreatic ductal adenocarcinoma (PDAC). While a pathologic complete response (pCR) to NT has been shown to be an important prognostic factor in single-institution studies, the incidence, characteristics, and outcomes of pCR have not been investigated in a population-based cohort of patients with PDAC.

Methods: Patients with localized PDAC and known cT and pT stage who received NT prior to pancreatectomy were queried using the National Cancer Database from 2004-2016. The clinical, demographic, socioeconomic, and hospital-related characteristics as well as long-term outcomes of patients who did and did not experience a pCR were compared.

Results: Among 7,902 patients who underwent NT prior to pancreatectomy, 244 (3.1%) experienced a pCR while 7,658 (96.9%) did not. Patients who experienced a pCR were younger (62.6 vs 63.9 years, p<0.05), had a longer duration of NT (200.5 vs 141.9 days, p<0.001), and were more likely to have advanced cT stage (T4: 26.2% vs 14.6%, p<0.001), cN0 stage (72.4% vs 66.4%, p<0.05) and to have received preoperative radiation (67.6% vs 47.3%, p<0.001). Median overall survival (OS) was longer among patients who experienced a pCR compared to those who did not (76.6 vs 26.0 months, p<0.001) (Figure). On multivariate cox regression analysis, a pCR was the strongest predictor of improved OS (HR 0.39, 95% CI 0.29-0.52). The OS of patients who experienced a pCR following neoadjuvant chemotherapy was similar to that of patients with a pCR following chemoradiation therapy (p=0.23).

Conclusion: The nationwide incidence and long-term outcomes of a pCR following NT for PDAC are similar to those reported in single-institution series. Given the significant association between pCR and OS, better predictors of response and more effective preoperative regimens should be aggressively sought.
76. DEFINING POSTOPERATIVE WEIGHT CHANGE FOLLOWING PANCREATECTOMY: FACTORS ASSOCIATED WITH DISTINCT AND DYNAMIC WEIGHT TRAJECTORIES

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Background: Weight change offers the simplest, global indication of a patient's surgical recovery, and is aligned with long-term quality of life. Yet, no studies have thoroughly investigated postoperative weight dynamics following pancreatectomy, with wide disparity amongst surgeons' perceptions of this concept. This study aims to define postoperative weight change dynamics following pancreatectomy and determine factors associated with optimal and poor weight trajectories.

Methods: From 2004-2019, 1,156 proximal (PD; 66%) and distal (DP; 34%) pancreatectomies were performed at a single institution for benign and malignant pathologies. Patient weights were acquired preoperatively and at postoperative months 1, 3, and 12. Optimal (Top Quartile, weight restoration) and poor (Bottom Quartile, persistent weight loss) postoperative weight cohorts were identified at 1-year. Multivariable analyses (MVA) were used to identify pre-, intra- and postoperative factors associated with these particular courses.

Results: The median percentage weight change (PWC) 1-year post-pancreatectomy was -7% (IQR: -2% to -13%), with similar median PWC between PD (-8.2%) and DP (-4.4%, p=0.568). Median weight loss primarily occurs within the first month and then plateaus thereafter. Just 19.4% of patients obtained their original weight within one year. No factors were significantly associated with postoperative PWC as a continuous variable, including: elderly age (>65) (p=0.495), obesity (p=0.409), preoperative diabetes or exocrine insufficiency (p=0.536; p=0.883, respectively), jaundice at presentation (p=0.492), malignancy (p=0.522), pre- or postoperative TPN/TEN (p=0.890; p=0.509, respectively), severe complications (p=0.627), adjuvant therapy (p=0.524), and tumor recurrence (p=0.368). Subsequently, weight restoration and persistent weight loss cohorts were analyzed (Figure 1). MVA revealed the independent factors associated with weight restoration were: non-elderly age (OR 1.73), non-obesity (OR 2.56), jaundice (OR 1.63), DP (reference: PD) (OR 2.34), not experiencing 30-day readmission (OR 1.61), and lack of tumor recurrence (OR 2.53). Conversely, persistent weight loss was associated with: elderly age (OR 1.51), obesity (OR 2.36), PD (OR 2.02), operative time>325minutes (OR 1.65), experiencing any complication (OR 1.68), receipt of adjuvant therapy (OR 1.44), and experiencing tumor recurrence (OR 5.46). Overall, 33% of the persistent weight loss cohort experienced tumor recurrence. Subset analysis of pancreatic adenocarcinoma patients (N=424, 37%) revealed factors associated with weight restoration to be: non-obesity (OR 2.95), DP (OR 1.74), estimated blood loss <400 (OR 1.71), not experiencing a severe complication (OR 5.73), and lack of recurrence (OR 2.32). For all patients, weight restoration was associated with longer median overall survival (31 vs. 18 months, p=0.039), while patients with persistent weight loss lived a median of 16 months.

Conclusion: These data define postoperative weight kinetics following major pancreatectomy, and identify optimal and poor weight trajectories. Overall, 80% of patients will not obtain their original weight, which may negatively impact their quality of life. Ultimately, weight restoration appears to be predetermined, driven by immutable characteristics. Persistent weight loss also appears to be inevitable due to demographic/pathological factors, particularly tumor recurrence, but may be mitigated by limiting operative time and complications. This study provides insight into post-pancreatectomy recovery, helping to guide patient expectations. Moreover, it offers a foundation for future studies directed towards nutritional optimization for pancreatic resections.
Weight Dynamics for Patients Undergoing Pancreatectomy

- Preoperation
- 1-Month Postoperation
- 3-Month Postoperation
- 12-Month Postoperation

Percentage Weight Change

- Weight Restoration Cohort
- Median Cohort
- Persistent Weight Loss Cohort