neoantigens, and decreased T-cell infiltration. Here, we use a novel strategy of increasing the mutational-burden of a Kras and P53 driven murine PC cell line, KP2, by treating it with DNA damaging chemotherapies, oxaliplatin and olaparib (OXPARPi). KP2 tumors have minimal T-cell infiltration and are extremely resistant to immunotherapy. We hypothesized that increased mutational-burden will promote T-cell infiltration, which will improve the efficacy of immunotherapy.

METHODS: We treated KP2 cells in vitro with OXPARPi. From the parental KP2-OXPARPi cell line, we generated multiple daughter cell lines, each with varying mutational burden and number of predicted neoantigens. We used subcutaneous and orthotopic models of PC to evaluate the effects of high mutational burden on T-cell infiltration and efficacy of immunotherapy (Fig.).

RESULTS: We observed significant reduction in tumor burden of KP2-OXPARPi tumors after treatment with immunotherapy (α-PD1+α-CTLA4) in subcutaneous and orthotopic models. In addition, depleting CD4+ and CD8+ T cells in KP2-OXPARPi tumor-bearing mice resulted in a significant increase in tumor growth.

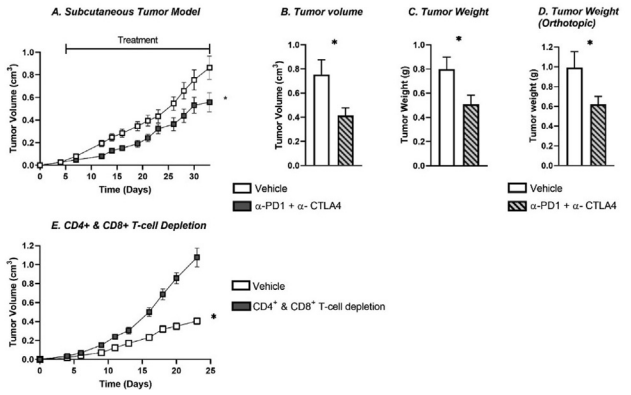

Figure. (A) Tumor growth curve (XY graph) in subcutaneous tumor model. (B).(C) Tumor volume arvd tumor weights (Bar graph) measured following treatment with vehicle and α-PD1 + α-CTLA4 on Day 33 N=10/group. (D) Tumor weights after 14-day treatment with α-PD1 + α-CTLA4 m an orthotopic model N=8-9/group (E) Tumor growth curve (XY graph) following CD4* and CD8* T-celi depletion in a subcutaneous tumor model N=10/group. *p<0.05.

CONCLUSIONS: Our data suggest that increasing the mutational-burden of PC has the potential to improve the efficacy of immunotherapy and this might be a useful strategy in the treating PC.

Inside Out Signaling of Sphingosine-1-Phosphate Promotes Hepatocellular Carcinoma Progression in Humans

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INTRODUCTION: Sphingosine-1-phosphate (S1P) is derived from cell-membrane sphigolipids by enzyme sphingosine kinase1(SphK1) in cytosol. It is transported out of cell by ABCC1 transporter, working in autocrine/paracrine fashion, including modulating tumor immune microenvironment. We have previously shown that high expression of SphK1 and ABCC1 (high K1C1) means higher levels of S1P outside of the cells. We hypothesize that high K1C1 will lead to progression of hepatocellular carcinoma and worse outcomes

METHODS: Patient cohorts from The Cancer Genome Atlas (n = 371) were used. We compared the set of patients with high K1C1 expression (n = 120) with that of low K1C1 expression (n = 119). Kaplan-Meier curves were used for disease-specific and overall survival.

RESULTS: We found significantly higher expression of SphK1 and ABCC1 in tumor vs normal liver and in aggressive tumors. The disease-specific survival ($p < 0.03$) and overall survival ($p < 0.003$) in high K1C1 group were significantly worse compared with low K1C1 group. In regard to tumor immune microenvironment, high group had higher tumor-associated lymphocytes, TCR Shannon and richness scores (increased cancer progression), also higher dendritic cells, Th2 cells CD4 T memory activated cells (anticancer activity). Gene Set Enrichment Analysis looking at mechanism of action, showed significantly enhanced cell proliferation (E2F targets, mTOR, G2Mcheckpoint, Myc) angiogenesis and increased aggressiveness (transforming growth factor-β, epithelial mesenchymal transition, Wnt-β-Catenin, IL6/JAK-STAT3).It also showed increased immune cell attraction, and anti-proliferation activity (increased apoptosis, p53).

CONCLUSIONS: S1P activates both pathways of cancer progression and anti-proliferation. However, the pro-cancer pathways overwhelm the anticancer pathways, leading to hepatocellular carcinoma progression. We conclude that high S1P levels promote growth and proliferation of hepatocellular carcinoma.

Laparoscopic vs Robotic Hepatectomy: A Propensity Score-Matched Analysis Accounting for Resection Complexity

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INTRODUCTION: Minimally invasive hepatectomy (MIH), including laparoscopic (LH) and robot-assisted hepatectomy (RH), is increasingly used for resection of liver tumors. The objective of this study was to compare outcomes of LH and RH using propensity score matching accounting for resection difficulty. This is the first comparative study to incorporate a validated laparoscopic liver resection difficulty score (LLRDS) in conducting the propensity score matching.

METHODS: Our study used a retrospective cohort of patients who underwent LH or RH for liver tumors between 2011 and 2019 at the University of Washington. The LLRDS was tabulated for each

resection and were assigned as either low, intermediate, or high difficulty. Patients were matched by propensity scores generated with the variables of age, sex, American Society of Anesthesiologists class, BMI, and numerical LLRDS.

RESULTS: A total of 326 MIHs were performed, including 100 LHs and 226 RHs. Of all MIHs, RH was performed more frequently for "high difficulty" hepatectomies compared with LH, 49% (112 of 226) vs 22% (22 of 100), respectively. After 1:1 propensity score matching, 92 patients from each cohort were included, with 68% (63) and 30% (28) of matched resections being "intermediate" and "high" difficulty, respectively. Mean operative time and estimated blood loss were significantly higher for RH compared with LH. Length of hospital stay, R0 resection rate and 30-day complication rate were similar between LH and RH (Table).

Table. Operative Outcomes

Outcomes	Laparoscopic (n = 92)	Robotic (n = 92)	p Value
Operative time, min, mean ± SD)	251 ± 99	309 ± 151	0.003
Blood transfusion in operating room, n (%)	3 (3.3)	6 (6.5)	0.5
Estimated blood loss, mL, mean ± SD)	150.9 ± 234.1	340.9 ± 465.3	< 0.001
Conversion to open, n (%)	3 (3)	0 (0)	0.08
Length of stay, d, mean ± SD)	2.7±1.6	2.9±1.5	0.45
R0 resection, n (%)	72 (78.3)	81 (88.0)	0.11
30-d complication, n (%)	4 (4.4)	10 (10.9)	0.16
30-d mortality, n	0	0	—

CONCLUSIONS: At our institution, RH was performed for more complex hepatectomies. When matched for LLRDS, improved intraoperative outcomes were observed during LH, but LH and RH had similar postoperative outcomes.

Mechanisms Underlying Ineffective Deep Vein Thrombosis Prophylaxis in Necrotizing Pancreatitis

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INTRODUCTION: Necrotizing pancreatitis (NP) patients have rates of venous thromboembolism (VTE) among the highest of any hospitalized patient (57%). We hypothesized that VTE prophylaxis might be inadequate in the setting of this profound inflammatory disease.

METHODS: All NP patients treated at a single center between August 2018 and December 2019 were enrolled in prospective, weekly VTE screening including 4-extremity duplex ultrasound. Routine chemoprophylaxis included low-molecular weight or unfractionated heparin. Peak serum anti-factor Xa concentration was measured during weekly screening (goal prophylaxis 0.2 to 0.4 IU/mL).

RESULTS: A total of 85 NP patients underwent a total of 201 screening events (mean 2.4 per patient). VTE developed in 50 patients (59%) including splanchnic vein thrombosis in 41 patients (48%) and extremity deep vein thrombosis (DVT) in 32 patients (38%). DVT was diagnosed a mean of 44 ± 5 days after NP onset. Pulmonary embolism was prevented in all patients diagnosed with DVT and no contraindication to anticoagulation (0 of 29). Prophylactic anti-Xa concentrations were only achieved in 21%; no DVT developed in patients achieving prophylactic anti-Xa concentration (Fig.).

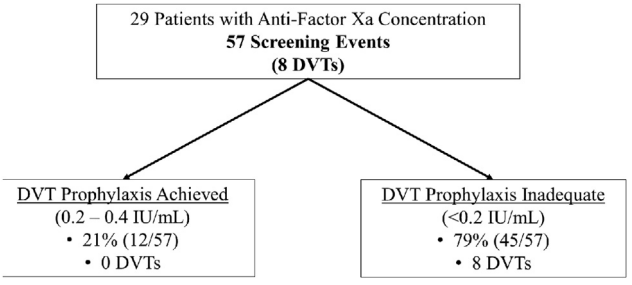

Figure.

CONCLUSIONS: In necrotizing pancreatitis patients, early identification of extremity deep vein thrombosis by screening ultrasound prevents pulmonary embolism. Fixed dosing of chemical prophylaxis is inadequate in most necrotizing pancreatitis patients and is the likely mechanism of increased venous thromboembolism in necrotizing pancreatitis.

National Trends and Perioperataive Outcomes of Robotic-Assisted Hepatectomy in the US: A Propensity Score-Matched Analysis from the National Cancer Database

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INTRODUCTION: A paucity of data exists on the national use of robotic hepatectomy. We assessed national trends and perioperative outcomes of robotic hepatectomy in the US. In addition, factors associated with the use of robotic approach were analyzed.

METHODS: The National Cancer Database was queried for patients undergoing hepatectomy (2010 to 2016). Trends of robotic utilization were assessed (Mantel-Haenszel test). Chi-Square/Mann-Whitney tests were used to compare variables. Factors associated with the use of robotic approach were assessed using logistic-regression MVA. Propensity score analysis was performed on patients undergoing robotic and open hepatectomy (controlling age, sex, Comorbidity Index, tumor size, stage, and surgical procedure).