Thyroid Cancer Neovasculature Expresses Prostate-Specific Membrane Antigen - A Possible Novel Therapeutic Target

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BACKGROUND: Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein receptor, is highly expressed in prostate cancers and in tumor neovasculature of colon, breast and neuroendocrine tumors. Here we analyzed PSMA expression in neovasculature of various thyroid cancer subtypes to assess the potential utility of PSMA as a predictor of aggressive malignancy and a potential therapeutic target.

METHODS: From a prospectively maintained database, we evaluated 91 samples from 68 patients, including 42 malignant primary thyroid cancers: [11 classic papillary (cPTC), 9 follicular-variant (FvPTC), 11 follicular (FTC), 6 radioactive iodine-refractory (RAIR), and 5 anaplastic (ATC) cancers], 9 distant and 12 lymph node metastases, 21 benign thyroid nodules, and 7 normal thyroids. Formalin–fixed paraffin-embedded tissue blocks were immunostained for vascular endothelial marker CD31 and PSMA with proper controls.

RESULTS: PSMA expression was not detected in normal thyroid tissue. Malignant tumors demonstrated a significantly higher PSMA expression than benign tumors (p<0.001). PSMA expression was seen in 38% of benign thyroid lesions, 79% of malignant thyroid lesions, and 100% of distant metastases. Of the malignant thyroid lesions, significant PSMA-positivity was noted in 100% of cPTC, 91% of FTC, 86% of RAIR cancers, 60% of ATC, and 44% of FvPTC. PSMA expression was higher in samples with distant metastases (100%) compared with samples with lymph node metastases (67%)

CONCLUSIONS: PSMA is significantly overexpressed in the neovasculature of thyroid carcinomas compared with normal and benign thyroid nodules. cPTC, FTC, and RAIR tumors demonstrated the highest percent of PSMA-positive samples. Furthermore, PSMA expression was seen in the neovasculature of all distant metastases. PSMA should be further explored as a novel diagnostic and therapeutic target for treatment of metastatic and radioiodine resistant thyroid cancers.
The Effect of Skin Pigmentation on Determination of Limb Ischemia
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ABSTRACT

INTRODUCTION Timely identification of tissue ischemia is critical, both in the traumatized limb and following free tissue transfer. The purpose is to determine if there is a difference in the ability of hand surgeons to diagnosis ischemia based on skin pigmentation.

METHODS A prospective study of healthy controls exposed to limb ischemia was conducted. The subjects were classified based on skin pigmentation using a defined skin type assessment tool, a visual color scale, and self-description of race. Patients were randomized by limb and tourniquet status; surgeons were blinded to both. Ischemia was induced by tourniquet insufflation and board-certified orthopaedic/plastic surgeons who had completed an accredited hand surgery fellowship conducted physical exams. The surgeons monitored the forearms at two, six, and ten minutes based on appearance of ischemia, capillary refill, and color in three locations in the limb (posterior interosseous artery (PIA) skin territory, radial forearm (RF) skin territory, and the digits).

RESULTS We found a significant difference in the ability to detect ischemia in patients with increased skin pigmentation, as documented by all metrics, when evaluating the PIA and RF flap at all time points. For example, when monitoring the PIA flap with the tourniquet insufflated at time 10 minutes, 92.9% of Caucasians were correctly identified as being ischemic whereas only 23.3% of African Americans were correctly identified(p<0.0001).

CONCLUSIONS There is a significant difference in the ability for board certified plastic and orthopaedic hand surgeons to correctly identify an ischemic limb with a physical exam based on the patient’s skin pigmentation.
Title: Activation of Hepatic Invariant Natural Killer T Cells Exacerbates Lung Inflammation and Apoptosis in Neonatal Sepsis

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Introduction: Neonates are particularly vulnerable to sepsis due to adaptive immune system immaturity and a reliance on passive immunity. The role of innate-like lymphocytes (ILLs) in this setting is of special interest. Invariant natural killer T (iNKT) cells, a subgroup of ILLs, rapidly produce cytokines following activation in adults. We hypothesized that iNKT cells would be activated to promote systemic inflammation and lung injury in neonatal sepsis.

Methods: Neonatal mice (5-7d) were subjected to sepsis by intraperitoneal (i.p.) injection of cecal slurry (CS) from adult mice. Sham pups received saline i.p. Ten minutes after CS injection pups received the α-galactosylceramide analog and iNKT stimulator KRN7000 (KRN, 0.2 µg/g body weight) or vehicle (2.5% DMSO in PBS) i.p. Ten hours later blood and tissue samples were obtained for analysis.

Results: Frequency of activated (CD69+) iNKT cells was increased from 7 to 13% in septic neonates compared to sham, and further increased to 16% with KRN treatment. Serum levels of IFN-γ and IL-1β were undetectable in sham pups and increased to 475 and 310 pg/ml, respectively, in septic pups, and 1028 and 439 pg/ml, respectively, after KRN treatment. In the lungs, IL-6 expression was increased 144- and 400-fold in septic and KRN-treated pups, respectively. Expression of neutrophil chemoattractants KC and MIP-2 was increased 127- and 143-fold, respectively, in septic neonates, with 231- and 308-fold increases following KRN treatment. The endothelial cell (EC) adhesion molecule VCAM-1 showed a 5-fold increase in expression after KRN treatment compared to sham. Finally, caspase-3 activity was increased 1.4-fold in septic neonates and 3.2-fold with KRN.

Conclusion: Hepatic iNKT cells are activated in neonatal sepsis. Further activation augments an increase in systemic and pulmonary inflammation, as well as chemokine expression, EC activation and apoptosis in the lungs. Our findings demonstrate the potential of iNKT cells as a therapeutic target in neonatal sepsis.
Patient Preferences for Venous Thromboembolism Prophylaxis After Injury

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Introduction: Limited evidence for the most efficacious venous thromboembolism (VTE) prophylaxis in orthopedic trauma has led to widespread variability in prescribed regimens. Understanding patient preferences towards costs, complication profile, and administration route is imperative in an era of patient-centered health care. This study used a discrete choice experiment (DCE) to determine patient preferences regarding VTE prophylaxis.

Methods: This prospective study enrolled adult orthopaedic trauma patients indicated for VTE prophylaxis at a Level-1 trauma center. Participants completed a DCE survey containing 10 hypothetical prophylaxis comparisons with varied attributes. Multinomial logit modelling was used to determine relative preferences and acceptable trade-off estimates for a 1% reduction in VTE complications or side effects.

Results: Of the 232 enrolled participants (mean age, 47.9 years; 56.9% male), patients most strongly valued a reduction in risk of death by pulmonary embolism (PE) (mean utility, 4.57; P<0.0001), distantly followed by risk of VTE (mean utility, 0.25; P<0.0001), wound complications (mean utility, 0.07; P<0.0001), and bleeding complications (mean utility, 0.05; P<0.0001). Patients preferred oral pills over subcutaneous injections (mean utility, 0.16; P<0.0001) but were willing to change their preference in favor of injections with a 6.98% absolute reduction in the risk of bleeding complications, a 4.53% absolute reduction in the risk of wound complications requiring reoperation, and a 1.27% absolute reduction in VTE risk. In contrast, only a 0.07% absolute reduction in risk of death due to PE was needed to change patients’ route preference. Underlying patient characteristics (sex, ethnicity, and type of injury) were associated with heterogeneity in preferences.

Conclusion: Orthopedic trauma patients prefer VTE prophylaxis by oral pill and are most concerned about the risk of death due to PE when choosing a regimen. The findings of this study are the first to document patient preferences with trade-off estimates in this important area of ongoing debate.

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Title: National outcomes for drainage of pancreatic pseudocysts: An analysis of nonoperative versus surgical approaches

Authors: Phoenix Vuong MD, Andrew Lowy MD, Jason Sicklick MD, Michael Bouvet MD

Introduction: Traditionally, open surgical internal drainage of pancreatic pseudocysts has been the primary treatment of choice via cystgastrostomy, cystduodenostomy, or Roux-en-Y cystjejunostomy. With advances in endoscopic instrumentation and skill base, endoscopic drainage has replaced surgical drainage as the preferred therapeutic modality.[1-3] However, new advances in laparoscopic drainage have been reported with increased success.[4-6] We compare outcomes of nonoperative vs. surgical drainage of pseudocysts.

Methods: The Nationwide Inpatient Sample (NIS) is the largest all-payer inpatient care database in the United States. Patients with diagnosis code for pancreatic pseudocysts were identified from 2006 through 2010. Patients with malignant neoplasms were excluded to ensure homogeneity of study population. Nonoperative drainage cases, including endoscopic and percutaneous drainage procedures, were identified and compared to surgical drainage cases. Outcomes of interest included postoperative complications, inpatient mortality, length of hospital stay, discharge disposition, and total charges. Continuous and categorical variables were compared by independent t-tests and Rao-Scott $\chi^2$ tests, respectively. Multivariate logistic regression was then performed on mortality and routine discharge rates to adjust for potential confounders.

Results: Of 43,292 admissions, 1,794 nonoperative and 1,179 surgical drainage patients were identified. Nonoperative management was more often selected in males (62.7% vs. 59.1%; p = .0384), emergent admissions (50.0% vs. 28.4%; p < .0001), and patients diagnosed with acute pancreatitis (61.0% vs. 35.0%; p < .0001), alcoholic cirrhosis (5.4% vs. 1.6%; p < .0001), or acute-on-chronic pancreatitis (13.3% vs. 9.5%; p = .0049). Nonoperative procedures were more often performed at nonprofit (20.3% vs. 15.0%; p = .0012) and nonteaching (66.4% vs. 72.2%; p = .0082) hospitals. Surgical drainage was performed more often in chronic pancreatitis (32.6% vs. 27.4%; p = .0034) or biliary tract disorders (29.2% vs. 19.3%; p < .0001). Surgical drainage was associated with increased gastrointestinal tract (5.4% vs. 3.0%; p = .0044) and intraprocedural complications (3.0% vs. 1.7%; p = .0099). However, nonoperative drainage had higher mortality (3.1% vs. 0.8%; p < .0001), longer hospital stays (19.4 vs. 13.6 days; p < .0001), increased hospital charges ($133,613 vs. $90,849; p < .0001), and were less often discharged routinely (58.3% vs. 76.1%; p < .0001). Adjusting for confounding variables, nonoperative drainage had a higher odds ratio for mortality (OR 2.60; p = .0182) and lower odds ratio for routine discharge (OR 0.53; p < .0001).

Conclusion: Despite recent trend towards endoscopic management of pseudocysts, surgical intervention for pseudocysts provides greater short-term outcomes even after adjusting for comorbidity differences. Data from longer follow-up periods and randomized comparative trials are needed. An interdisciplinary approach is best suited for the safe and effective stage-specific treatment of pancreatic pseudocysts.
The Intravenous Application of CXCR4-Targeted Conditionally Replicative Adenovirus with Fiber and Hexon Modifications in Pancreatic Cancer

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Introduction:
Cancer stem cells (CSC) have been shown to be involved in the development of pancreatic ductal adenocarcinoma (PDAC). We previously developed conditionally replicative adenovirus (CRAd) that targets PDAC cells that overexpress the CSC marker CXCR4. Fiber modification to this CRAd showed enhanced viral replication in xenografts. However, sequestration by liver or lung may affect the systemic delivery of the virus. The aim of this study is to determine whether additional structural modifications to CXCR4-targeted adenovirus can reduce sequestration to enhance delivery to tumor in preclinical models.

Methods:
The CXCR4 promoter-driven CRAd with chimeric fiber (Ad5/3) was additionally modified with the substitution of Ad5 hexon with Ad3 hexon and peptide insertions in the Ad3 hexon hypervariable regions 5 and 7. The distribution of the hexon-modified and fiber-modified adenovirus was assessed with PCR viral copy number assay and expression of major late promoter-driven luciferase after systemic injection in hamsters. Antitumor effect was assessed after intratumoral and intravenous injections in patient-derived PDAC xenografts on SCID mice.

Results:
The viral copy number assay showed decreased liver sequestration with hexon modification in hamsters. The luciferase assay showed more significant reductions in liver and lung. After intratumoral injections, the hexon and fiber-modified adenovirus showed significantly increased antitumor effect, compared to non-modified adenovirus (p<0.05). After intravenous injection, only the CRAd with hexon and fiber modifications showed significant antitumor effect, compared to both fiber-modified adenovirus (p<0.005) and non-modified adenovirus (p<0.05).

Conclusion:
The addition of hexon modification to a fiber-modified CXCR4 targeted CRAd is effective in PDAC and shows decreased sequestration in preclinical models.

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Title: Risk Factors Associated with Suicide in Hepatobiliary Malignancy

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Institution: Medical College of Georgia at Augusta University

Introduction:

Increased suicidal tendencies among cancer patients have been well documented. To date there has been no specific examination of suicide rates and factors associated with suicide in hepatobiliary malignancy. The aim of this study is to examine suicide incidence and associated factors in hepatic, gallbladder and other biliary malignancy patients.

Methods:

The Surveillance, Epidemiology, and End Results (SEER) Database of the National Cancer Institute was queried to identify patients with hepatobiliary malignancies. The study included mortality and demographic data from 1973 to 2013. Comparison data with the general US population was derived from the Centers for Disease Control and Prevention’s National Center for Injury Prevention and Control using the Web-based Injury Statistics Query and Reporting System. Standardized mortality ratios (SMRs) and their 95% confidence intervals (95% CIs) were calculated and generated odds ratios (ORs) for the identification of factors associated with suicide for hepatobiliary malignancy.

Results:

For liver malignancies 68 suicides among 108,862 patients were identified. For gallbladder and other biliary malignancies 13 suicides among 22,002 patients. For liver cancer, patients with male gender were found to have a statistically significant higher suicide rate p <0.001, OR 15.7 (95% CI 3.86-64.1). Marital status was also statistically significant p = 0.0127, with the highest frequency being married patients. For gallbladder cancers, patients with male gender p <.0001, OR 14.49 (95%CI 3.243-64.781) were more likely to commit suicide. The SMRs for patients with liver cancer were 2.04 for males (95% CI, 1.63-2.57), 3.33 for African-Americans (95% CI, 1.69-5.94), 3.41 for Caucasians (95% CI, 2.61-4.38). The SMRs for patients with gallbladder cancer were 3.20 for females (CI 0.54-10.56), 3.41 for males (CI 1.85-5.80), 1.42 for African Americans (0.07-7.01) and 2.21 for Caucasians (CI 1.16-3.83).

Conclusion:

Identification of evidence-based risk factors associated with suicide among patients with hepatobiliary malignancy is an important step in the development of screening strategies and management of psychosocial stressors. This study identifies males with hepatobiliary malignancies with significantly increased odds of committing suicide.
Do long acting local anesthetics decrease the need for postoperative narcotic use in outpatient hernioplasty?
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Introduction:
Prescription narcotic misuse is now an epidemic in the United States. This study set out to examine whether liposomal bupivacaine (Exparel), 0.25% bupivacaine (Marcaine), or 1% lidocaine with epinephrine mixed with 0.25% bupivacaine would decrease the postoperative use of narcotics in ambulatory hernioplasty.

Methods:
A single surgeon at our institution performed 427 consecutive tension-free plug and patch mesh hernia repairs under local anesthesia with IV sedation from April 1, 2015 to December 31, 2015. Hernia repairs included inguinal, ventral, incisional, and umbilical. In 9.3% of cases two hernias were repaired during the same procedure. Every patient was seen between six and eleven days post hernioplasty and a standardized pain questionnaire was completed regarding subjective pain, prescription “painkiller”, and over the counter pain medication use in both quantity and duration. The primary endpoint was percentage of patients not requiring narcotics for pain control.

Results:
The Exparel group (147) and the Marcaine group (144) had similar results at 59% and 55% of patients who were able to avoid postoperative narcotics completely. The commonly used lidocaine with epinephrine/Marcaine mixture had only 39% success rate, significantly lower than the other groups. Included in the study were patients that had two simultaneous hernia repairs where the exparel group only had 5.4% with 14% in the Marcaine.

Conclusion:
Our study demonstrates Exparel and Marcaine performed similarly reducing the need of postoperative narcotic use in outpatient hernia surgery by over 50%. Both were a considerably better option than the Lidocaine/Marcaine mixture. The average cost difference between Exparel and Marcaine is exponential, with a difference of over 200 dollars per patient. Marcaine provides a significant cost benefit while achieving similar if not better postoperative pain relief and reduces postoperative narcotic use. Marcaine has become the standard of care in our hernia center.

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Frailty adversely impacts long-term survival and limb salvage after lower extremity revascularization

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**Introduction:** Frailty is a geriatric syndrome associated with poor surgical outcomes. Our aim was to evaluate the relationship between frailty, biomarkers of frailty, and long-term outcomes in peripheral arterial disease (PAD) patients undergoing first-time lower extremity revascularization.

**Methods:** A retrospective chart review was performed on all patients undergoing first time lower extremity revascularizations over a 10-year period at a single institution. A total of 199 patients were included. Frailty was measured using a modified frailty index (mFI) previously validated in vascular surgery patients. Composite risk models of mFI score, demographic and serologic biomarkers of frailty were created to predict surgical outcomes. Primary end-points were 30d and 1y mortality, 1y limb salvage, and 30d morbidity and readmission rates. Secondary endpoints assessed were length of hospital stay (LOS) and disposition at discharge.

**Results:** Kaplan Meier Curves demonstrated that the highest mortality (p=0.013) and amputation (p=0.007) rates occurred in the most frail patients. Both readmission rates (p=0.003) and LOS (p=0.006) were associated with frailty. Overall morbidity was increased in patients with higher mFI (p<0.001). Discharge disposition was not significantly correlated with frailty (p = 0.90) but correlated with procedure type (p= 0.05) and age (p=0.004). Univariate analysis of biomarkers and anthropomorphic measures showed significant correlations between mFI score and low Hgb (p < 0.001), eGFR (P= 0.42), and low albumin (p= 0.077) levels. Multivariate analysis identifies frailty (HR=1.5; 95% CI 1.04 – 2.16) and age (HR 2.03; 95% CI 1.01 – 4.08) as independent predictors of amputation. The 24-month survival risk model similarly showed that higher mFI (HR = 1.628: 95% CI 1.123 -2.359) was predictive of mortality.

**Conclusion:** Frailty severity scores are associated with increased risk of long-term amputation and mortality after first-time lower extremity revascularization. Routine pre-operative lab tests may serve as objective, independent biomarkers of frailty in patients with PAD.

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The Identification and Treatment of Intestinal Malrotation in Older Children

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INTRODUCTION

Intestinal malrotation is often a diagnosis of infancy. However, the true incidence outside of this age is unknown, as these patients often present atypically or are diagnosed intra-operatively. We sought to evaluate the incidence, clinical presentation, ideal imaging and intra-operative findings of patients diagnosed with malrotation over 1 year of age.

METHODS

A retrospective review was conducted in patients older than one year of age who were treated for malrotation at a single pediatric tertiary care center between 2000 to 2015. Data analyzed included age at presentation, presenting symptoms, imaging performed, intraoperative findings and postoperative follow-up. Patients predisposed to malrotation were excluded.

RESULTS

246 patients were diagnosed with malrotation; 77 (31%) were found to be older than one year of age. Of these, 25% were found incidentally during investigations for other disease processes. The most common presenting symptoms were vomiting (68%), abdominal pain (57%), reflux (18%), bilious vomiting (17%), constipation (17%) and failure to thrive (14%). 56% of patients had previous similar symptoms. The method leading to diagnosis included UGI (61%), CT (26%), intra-operative finding (6.5%) and other diagnostics (6.5%). Of the sixty patients obtaining an UGI: 83% revealed “malrotation”, 13% were “suspicious for” malrotation and the remainder was non-diagnostic. Of those radiologically diagnosed, 75 had surgical intervention with 97% confirmed to have malrotation. Intra-operatively, 60% were found to have a malrotated intestinal orientation, 33% with non-rotation, and 1% with reverse rotation. 22% patients were obstructed with 12% having a volvulus. Of the 68 patients with postoperative follow up, 59% reported alleviation of symptoms, 15% remained asymptomatic, and 26% had persistence of preoperative symptoms.

CONCLUSIONS

Malrotation should be on the differential despite age given the highly variable clinical presentation. An UGI should be conducted first for a prompt diagnosis and surgical correction should be undertaken despite atypical presenting symptoms.