UNIVERSITY OF WISCONSIN

18th Annual Resident Research Day

May 16

2018

10:00am

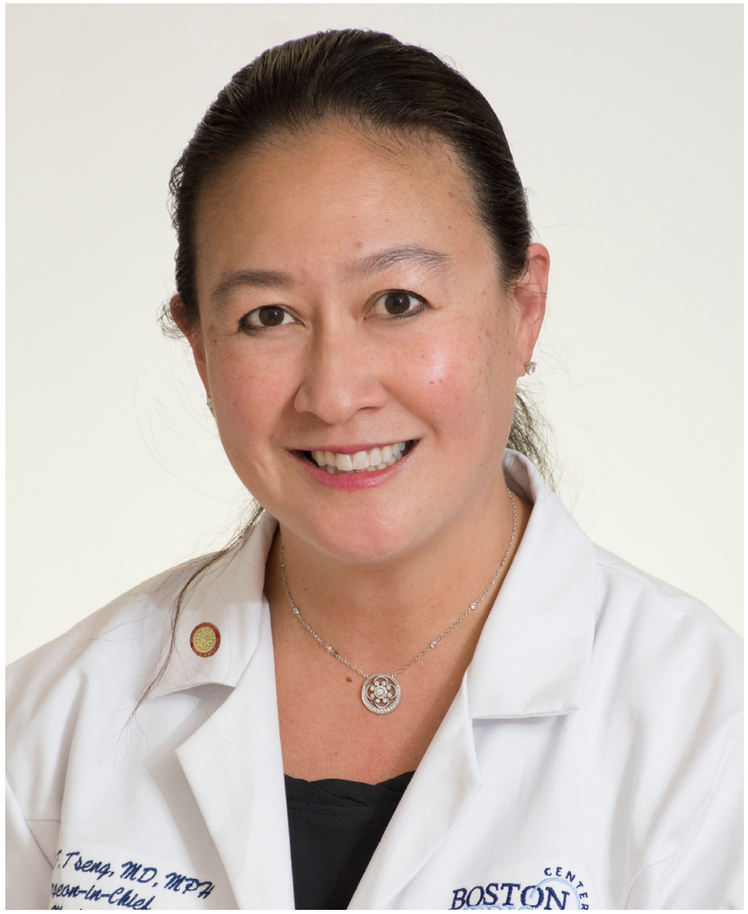
Health Sciences Learning Center

Rm 1345

Visiting Professor

Jennifer Tseng, MD, MPH

Utley Professor and Chair
Department of Surgery
Boston University School of Medicine
Surgeon-in-Chief at Boston Medical Center



Jennifer F. Tseng, MD, MPH, is the *Utley Professor and Chair* of the Department of Surgery at Boston University School of Medicine, and *Surgeon-in-Chief* at Boston Medical Center in Boston, Massachusetts.

Dr. Tseng is an acclaimed surgical oncologist and gastrointestinal surgeon whose practice focuses on the upper gastrointestinal tract. Prior to being recruited to Boston University School of Medicine/Boston Medical Center in July 2017, Dr. Tseng served as the chief of surgical oncology at Beth Israel Deaconess Medical Center (BIDMC) and as a professor of surgery at Harvard Medical School. Of note, Dr. Tseng was the first female full professor of surgery at BIDMC and only the fourth in the history of Harvard Medical School. While at BIDMC, she led a diverse group of faculty in oncology research, education, and care for gastrointestinal, endocrine, breast, melanomas and sarcomas, and other malignancies.

Dr. Tseng has published more than 120-peer reviewed journal articles on reducing surgical risk, cancer biomarkers, and developing models for cancer treatment-sequencing strategies, with a strong focus on racial and socioeconomic disparities in care. She has worked with the Massachusetts Department of Public Health to assess the impact of factors including insurance, social disparities, and health care reform on cancer diagnosis, treatment, and prevention. Dr. Tseng is on the editorial board of several journals and as of January 1, 2018 was appointed Deputy Editor of *JAMA Surgery*.

Prior to her tenure at BIDMC, Dr. Tseng was the founding director of SOAR (Surgical Outcomes Analysis & Research) at the University of Massachusetts Medical School, a research initiative to improve treatment strategies for a broad range of surgical conditions and to develop tools to assess and reduce risk. She and her co-leaders at BIDMC continued the development of SOAR as a health services and outcomes research group, which has now been transitioned to BU/BMC as Boston SOAR.

Dr. Tseng received her undergraduate degree from Stanford University, her MD from the University of California, San Francisco Medical School, and her MPH from the Harvard T. H. Chan School of Public Health. She completed a general surgery residency at Massachusetts General Hospital and a research fellowship in molecular medicine at Harvard Medical School/Boston Children's Hospital, followed by a clinical fellowship in surgical oncology at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Tseng assumed her position at Boston University School of Medicine and Boston Medical Center on July 1, 2017. Dr. Tseng is the first woman to serve as chair and chief of surgery at an academic medical center in Boston, and one of only a small percentage nationally.

Agenda

Grand Rounds Presentation

Health Sciences Learning Center, Room 1345

AM

6:30 **Can health policy help eradicate disparities in cancer care?** **Page 2**
Jennifer F. Tseng, MD, MPH, Visiting Professor – Boston University

Resident Research Presentations

Health Sciences Learning Center, Room 1345

10:00 **Introduction and Welcome**
Jacob Greenberg, MD, EdM

10:15 **What do you want to know? How surgical experience predicts the types of questions asked in a didactic CME course** **Page 5**
Martha Godfrey, MD — Discussant: Eugene Foley, MD

10:30 **Stakeholder views of organ donation before circulatory death for patients who do not meet brain death criteria** **Page 7**
Christopher Zimmerman, MD — Discussant: David Foley, MD

10:45 **Direct Radiologic-Pathologic Correlation of Colorectal Liver Metastases with MR-Compatible Sectioning and Localization Device** **Page 9**
Victoria Rendell, MD — Discussant: David Foley, MD

11:00 **Evaluating the Impact of Pre-Transplant Malignancy on Outcomes after Kidney Transplantation: A National Transplant Database Analysis over a Twenty-Two Year Period** **Page 11**
Devon Livingston-Rosanoff, MD, PhD — Discussant: Sean Ronnekliev-Kelly, MD

11:15 **Chromogranin A and Predicting Recurrence in Pancreatic Neuroendocrine Tumors: A Novel Pre-Operative Risk Scoring System** **Page 13**
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11:30	**Topical Application of a Dual PI3K/mTOR Inhibitor for the Prevention of Anal Carcinogenesis In Vivo** Brooks Rademacher, MD — Discussant: Cristina Geltzeiler, MD	**Page 15**
11:45	**BLyS Deficient Rats Prevent Donor Specific Antibody Production and Proliferation in Rodent Model** Natalie Bath, MD — Discussant: Joshua Mezrich, MD	**Page 17**
PM		
12:00	LUNCH (HSLC Atrium)	
1:00	**Prolongation Of Skin Allograft Survival Through Dietary Supplementation of Ayrl Hydrocarbon Receptor Ligands** Amin Afrazi, MD, PhD — Discussant: William Burlingham, PhD	**Page 18**
1:15	**Multi-scale Structure-Function Relationships in Right Ventricular Failure Due to Pressure Overload** Jenny Philip, MD — Discussant: Kara Goss, MD	**Page 19**
1:30	**Targeted Donor Complement Blockade After Brain-Death Prevents Delayed Graft Function But Not Progression To Antibody-Mediated Rejection In A Non-Human Primate Model Of Kidney Allo-Transplantation** Juan Danobeitia, MD, PhD — Discussant: David Al-Adra, MD, PhD	**Page 20**
1:45	**Perioperative Outcomes After Extremity Sarcoma Resection - Results of a Contemporary Multi-Institutional Experience** Kara Vande Walle, MD — Discussant: Sharon Weber, MD	**Page 22**
2:00	**Natural Language Processing for Thyroid Pathology Reports: Does Synoptic Reporting Improve Information Retrieval?** Joseph Imbus, MD — Discussant: Rebecca Sippel, MD	**Page 24**
2:15	**A Randomized Controlled Trial Evaluating Receipt of Decision-Aid and Patients' Perception of Information Conveyed During Surgical Consultation** Trista Stankowski-Drengler, MD — Discussant: Susan Pitt, MD	**Page 26**

Abstracts

What do you want to know? How surgical experience predicts the types of questions asked in a didactic CME course

Martha Godfrey, Alexandra A. Rosser, Carla Pugh, Ajit Sachdeva, Sarah Sullivan

Background
Surgeons taking continuing medical education (CME) courses possess a wide variety of backgrounds and surgical experience. As such, these surgeons may have very different learning needs which can be measured by the types of information requested by participants. This study examines the relationship between surgeons' levels of operative experience and what types of questions they asked in the context of a CME course.

Methods
Audio-video data were collected from surgeons (n=29) participating in a simulated laparoscopic hernia repair CME course. Participants were grouped in teams of three according to their self-reported laparoscopic and hernia repair experience and performed different forms of laparoscopic hernia repairs across two separate learning sessions. Their recorded conversations were then coded for the presence of four types of questions they asked their instructors. We computed the percentages associated with how often each type of question was asked for each participant. Finally, we performed linear regressions comparing how often these questions were asked based on the participants' self-reported levels of experience.

Results
Standard linear regressions of types of questions participants asked revealed significant differences between surgeons' of relatively lesser and greater experience with regards to three types of questions: Requesting Guidance, Requesting Confirmation, and Asking About a Specific Case. Both Requesting Guidance and Requesting Confirmation were inversely proportional to surgical experience, whereas Asking About a Specific Case was directly proportional to surgical experience. Requesting Instructor Preference, on the other hand, exhibited no significant correlation with participants' levels of experience, FIGURE 1.

Conclusion
Surgeons learning in a CME context exhibit statistically different needs as demonstrated by the types of information they request from their instructors; those with relatively less experience tend to focus on asking for confirmation and guidance, whereas those with relatively greater experience tend to focus on specific hypothetical scenarios related to their practice. This study not only gives insight into the learning needs of surgeons in CME courses, but also provides data that can be used to train the trainer by offering guidance on ways to tailor instruction to focus on content that learners of a particular level will benefit from most.

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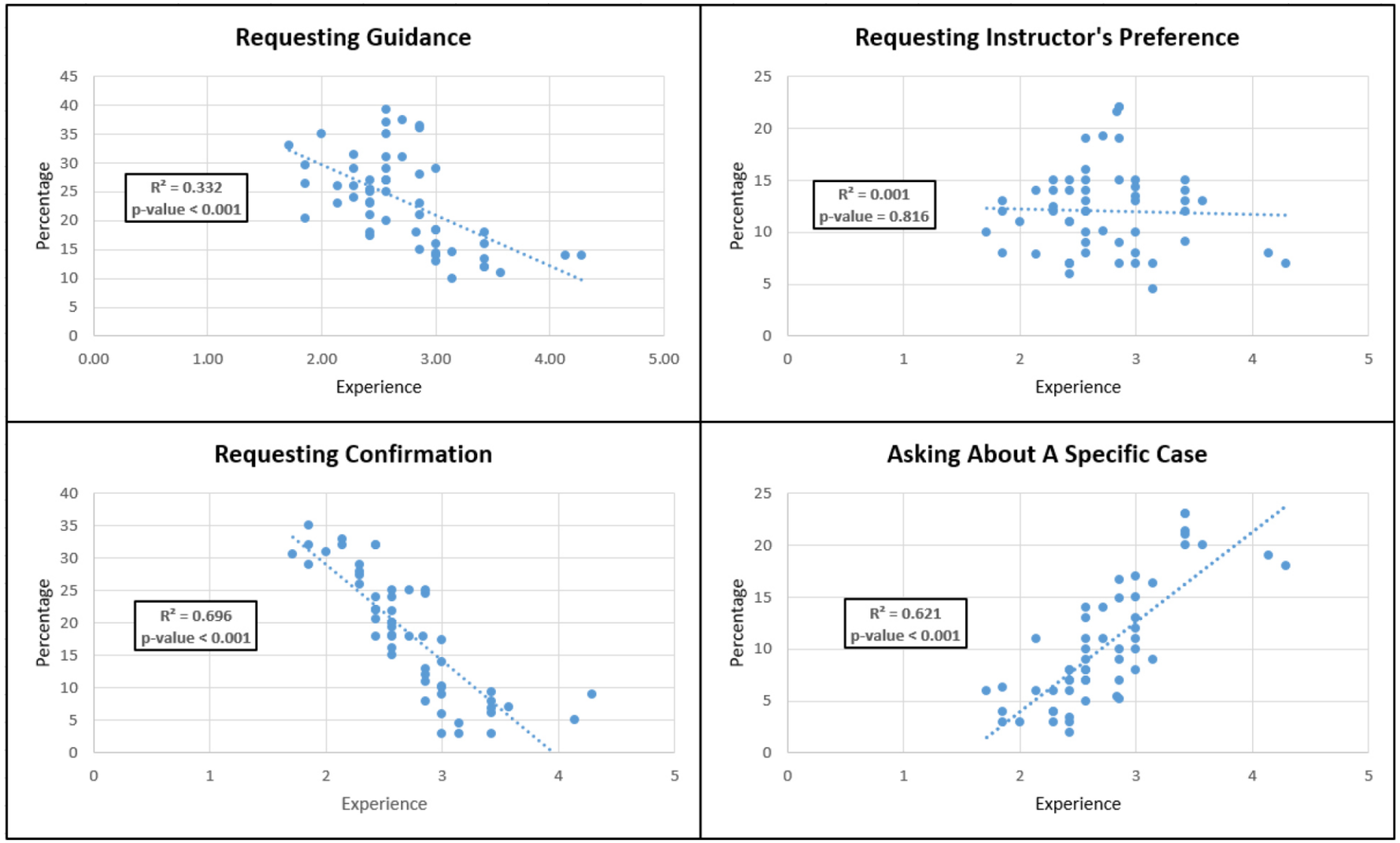
Abstracts

FIGURE 1



Abstracts

Stakeholder views of organ donation before circulatory death for patients who do not meet brain death criteria

Baggett ND, **Zimmermann CJ**, Taylor LJ, Buffington A, Scalea J, Fost N, Croes KD, Mezrich JD, Schwarze ML

Introduction
There is an unmet need for strategies to permit imminently dying patients to donate organs. The objective of this study is to characterize attitudes about one novel strategy, donation before circulatory death, from the viewpoint of organ-donor families and professional stakeholders.

Methods
We interviewed families (n=15) who had experienced unsuccessful donation after circulatory death (DCD) and conducted six focus groups at national meetings with professionals including clinicians, policy makers, and procurement personnel involved with organ donation. We used qualitative content analysis to characterize concerns and support for organ recovery strategies before cardiac death specifically comparing procurement of "just a kidney" to "all organs."

Results
All families described significant harms associated with unsuccessful DCD and many expressed support for organ recovery prior to cardiac death. Professional stakeholders were strongly opposed to recovery of all organs and equated this strategy with "murder." They were more supportive of single kidney recovery because nephrectomy was unlikely to cause the death of the donor. Stakeholders stressed the critical importance of public support for organ donation, the value of brain death and the dead-donor rule as a facilitator of organ donation, and expressed concern that consideration of alternate recovery strategies would harm the existing transplant system. First-person consent was described as a logistical challenge but achieving consent could mitigate some, but not all, ethical concerns.

Conclusion
There is much at stake in consideration of novel strategies for organ recovery, yet these findings highlight the potential tolerability of single kidney recovery before cardiac death.

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Abstracts

Table 1. Selected family and professional stakeholder responses to alternative organ donation strategies.

Description	Quotes
Many family members expressed regret about their loved one's inability to donate through the DCD pathway and suggested donation before circulatory death was an acceptable way to fulfill their loved one's wishes.	*…if they could have just said, "OK, we're just going to do it. He's going to die. As soon as we pull his heart, these are the things that are going to happen." I think we— I can say pretty certainly we all would have been OK with that. That was what, at that point in time, it was all about organ donation for us.*
	Um, I would still say, morally, you're only removing one kidney. That's not going to take her life. I would still say, morally, that it would be the thing to do.
Professional stakeholders viewed donation of "all organs" prior to cardiac death as murder.	*Because this is the ultimate harm. You are taking an action to stop a life, you know. I mean, there's a knife involved here and a clamp, and I can't see how we could write a policy that would ever cover for that scenario.*
	Because with donating one kidney, you can still live. With donating all your organs, there is no way. I mean, this is definitely, this is unethical I think.
Professional stakeholders viewed recovery of "just a kidney" as more tolerable than "all organs" because the act of donation prior to declaration of cardiac death was unlikely to harm or cause the immediate death of the donor.	*She can [live] with one kidney and most of her liver. You're not, you're not taking away her ability to survive by taking those organs.*
	Well, I would really believe that this person does not have any hope of a viable life, maybe a persistent vegetative state, and I would ethically feel fine with removing a kidney.

Abstracts

Direct Radiologic-Pathologic Correlation of Colorectal Liver Metastases with MR-Compatible Sectioning and Localization Device.

Victoria Rendell, MD, Timothy Colgan, PhD, Gesine Knobloch, MD, Agnes Loeffler, MD, PhD, Scott Reeder, MD, PhD, and Emily Winslow, MD, MS

Background
Patients with colorectal cancer liver metastases derive a significant survival benefit from resection. However, small indeterminate lesions on pre-operative imaging remain problematic for surgical planning. Precise radiologic-pathologic correlation of these small lesions would improve radiologic characterization, although this has proved challenging. We developed an MR-compatible sectioning device to allow precise correlation of radiologic lesions in tissue during sectioning. Having validated this method in a porcine model, we aimed to establish the feasibility of our method in resected human liver specimens and to determine the performance of the intraoperative administration of the liver-specific contrast agent, gadoxetic acid, in ex vivo liver imaging.

Methods
Patients undergoing liver resection at UW Hospital were consented to one of three groups related to intraoperative administration of gadoxetic acid: 1) none; 2) 0.025 mmol/kg; and 3) 0.05 mmol/kg (standard dose). Contrast was administered prior to vascular inflow ligation. Once removed, the specimen underwent gross inspection and inking and was then stabilized in the 27 x 14 x 14 cm3 Plexiglas sectioning device featuring three MR-visible silicone gel grids and corresponding slicing channels designed to facilitate radiologic-pathologic correlation. The device was then transported to a 3T MR scanner, and high-resolution T1-weighted fast spoiled gradient echo and T2-weighted fast-spin-echo MR images were acquired using a single channel quadrature head coil. A study radiologist noted the location and size of all lesions identified on MR imaging. The specimen was then sectioned using the radiologic coordinates and the device's slicing channels to identify lesions. A final histopathologic diagnosis was obtained for all tissue corresponding to the radiologic coordinates. Accuracy of lesion identification using this method was calculated.

Results
Since February 2018, when IRB approval was granted, 5 patients have enrolled in the following groups: no contrast (n=1), 0.025 mmol/kg contrast (n=2), and 0.05 mmol contrast (n=1). One patient did not complete the study due to an intraoperative decision to ablate rather than resect. In total, 17 lesions were identified radiologically.

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Abstracts

Results *(cont'd)*
12/12 (100%) of radiologically identified lesions corresponded to lesions pathologically. Five lesions are awaiting final pathologic diagnosis. Figure 1 demonstrates the precise correlation during gross sectioning of two lesions identified on ex vivo MR imaging. The time intervals between contrast administration and vascular ligation/Pghringle maneuver were 6, 9, and 18 minutes. Gadoxetic acid contrast enhancement was present on all images obtained after contrast administration, and the longest time interval between contrast administration and imaging was 3 hours.

Conclusions
Early results are promising that this radiologic-pathologic correlation method is feasible and precise when incorporated into the clinical environment. Intraoperative administration of the gadoxetic acid resulted in contrast enhancement of the liver parenchyma on ex vivo imaging several hours later. Since gadoxetic acid improves sensitivity of small lesion identification, this technique is likely to be useful in further work to improve radiologic characterization of small indeterminate hepatic lesions.

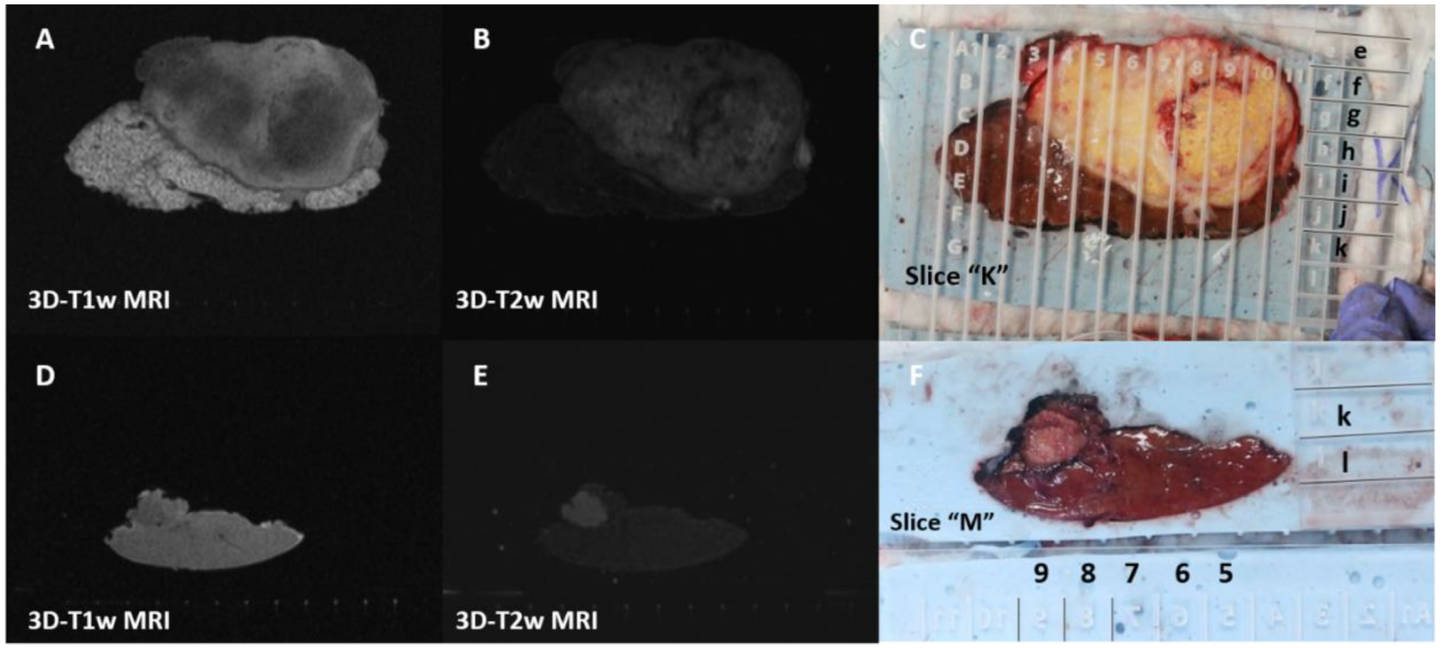

Figure 1. Radiologic-pathologic correlation of colorectal liver metastases. Resected liver specimens are stabilized in a radiologic-pathologic correlation device and 3D- T1 and T2 weighted MR images (MRI) are obtained. The device's MR-visible 3D grid allows precise localization of lesions during sectioning (**C** and **F**). Contrast enhancement from intraoperative contrast administration is visible on T1-weighted images for the specimen in **A-C**. The patient whose specimen is shown in **D-F** received no contrast. The radiologic coordinates for the lesion shown in **A-C** were "G-O, 3-11, e-k" and for the lesion in **D-F** were "L-M, 8-9, k-l."

Abstracts

Evaluating the Impact of Pre-Transplant Malignancy on Outcomes after Kidney Transplantation: A National Transplant Database Analysis over a Twenty-Two Year Period

Livingston-Rosanoff D, Leverson G, Foley DP, Wilke LG

Introduction
Patients with a history of malignancy prior to kidney transplantation (KTx) have historically been identified as having an increased risk of post-transplant malignancies and inferior outcomes. There have been no recent large studies examining trends and outcomes in transplanted patients with prior skin and non-skin malignancies. The purpose of this study was to determine the impact of pre-transplant malignancy (PTM) on 1) patient and graft survival and 2) the development of post-transplant malignancy.

Methods
We queried the Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS) database for all primary KTx recipients from 1994-2016. Patients were stratified by diagnosis of PTM and type of kidney transplant (deceased vs. living donor). The development of post-transplant malignancy, patient survival, graft failure (GF), and death censored graft failure (DCGF) rates in patients with and without PTM were compared using Cox proportional hazard and log-rank analyses. Pre and post-transplant malignancy diagnoses included all types of skin and non-skin malignancies.

Results
Since 1994, both the number and frequency of kidney transplants performed in patients with PTM increased from <1% of all kidney transplants in 1994 (n=77) to 8.3% in 2016 (n=1,329) (Fig. 1). This trend was true for all PTMs including non-skin cancer malignancies. KTx recipients with PTMs were older (60 + 11y) and more likely to be Caucasian (72%) than those without PTM (50 + 13y and 50.5% respectively). PTM patients experienced increased GF (HR 1.25, CI 1.22, 1.28), but decreased DCGF (HR 0.84 CI 0.80, 0.88). In multivariate models, PTM was not associated with DCGF (HR 1.03 CI 0.98, 1.08), but was independently associated with increased mortality (HR 1.11 CI 1.08, 1.15) and more post-transplant malignancies (HR 2.19 CI 2.01, 2.38). When skin cancers were removed from the multivariate analysis, DCGF was similar between patients with or without PTM (HR 1.04 CI 0.99, 1.09). However non-skin cancer PTM was independently associated with increased mortality (HR 1.15 CI 1.11, 1.19) and increased post-transplant malignancy (HR 1.78 CI 1.61, 1.97).

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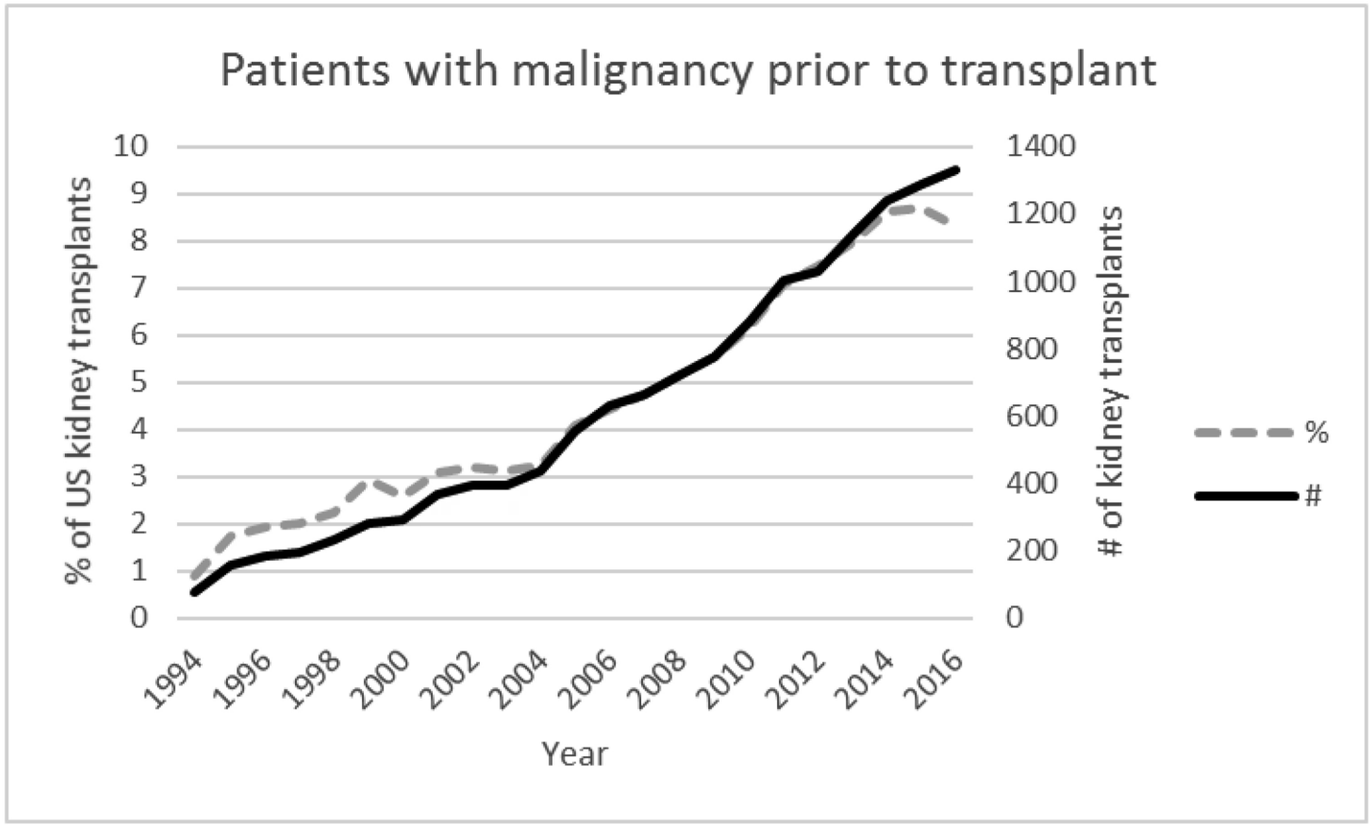
Abstracts

Conclusions

Over the last 22 years, more patients with a pre-transplant malignancy are receiving KTx in the United States. Patients with PTM overall have similar death censored graft failure but worse patient survival, a higher risk of post-transplant malignancy and increased overall graft failure compared to those without PTM. Patients with non-skin cancer malignancies prior to transplant experience a decrease in patient survival, but no difference in death censored graft failure. This analysis suggests that the current practice of performing kidney transplantation in patients with PTM provides equivalent graft survival to those without a prior malignancy with however an increased risk of post-transplant malignancy in comparison to those without PTM.

Figure 1: Increasing rate of kidney transplantation in patients with PTM



Abstracts

Chromogranin A and Predicting Recurrence in Pancreatic Neuroendocrine Tumors: A Novel Pre-Operative Risk Scoring System

Alexander V. Fisher, MD[1], Alexandra G. Lopez-Aguiar, MD[2], Victoria R. Rendell, MD[1], Courtney Pokrzywa, BA[1], Flavio Rocha, MD[3], Zaheer Kanji, MD[3], George Poultsides, MD[4], Eleftherios Makris, MD[4], Mary Dillhoff, MD[5], Eliza Beal, MD[5], Ryan C. Fields, MD[6], Roheena Panni, MD[6], Kamran Idrees, MD[7], Paula M. Smith, MD[7], Clifford Cho, MD[8]; Megan Beems, MD[8], Shishir K. Maithel, MD[2], Emily R. Winslow, MD[1], Daniel E. Abbott, MD[1], Sharon M. Weber, MD[1]

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3. Department of Surgery, Virginia Mason Medical Center, Seattle, WA
4. Department of Surgery, Stanford University Medical Center, Stanford, CA
5. Division of Surgical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH
6. Department of Surgery, Washington University School of Medicine, St Louis, MO
7. Division of Surgical Oncology, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN
8. Division of Hepatopancreatobiliary and Advanced Gastrointestinal Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI

Introduction
Chromogranin A (CgA) may be prognostic for patients with neuroendocrine tumors. However, the value of incorporating CgA level into pre-operative risk stratification has not been evaluated in a large multi-institutional study.

Methods
Patients undergoing resection for pancreatic neuroendocrine tumors (pNET) were selected from the 8 institutions of the US Neuroendocrine Tumor Study Group database. Of 296 patients, a stratified random sample of 232 (78% of cohort) was used for risk score development, with the remaining 64 (22%) used for risk score validation. Patients were grouped by CgA level in reference to the upper limit of normal (ULN) as follows: normal, 1-5x ULN, and >5x ULN. Cox regression was used to identify pre-operative variables that predicted recurrence-free survival (RFS), and those with p<0.1 were included in a risk score. Logistic regression was used to evaluate the risk score for predicting tumor recurrence in the validation cohort.

Results
In the entire cohort, 251 (85%) patients had localized pancreatic tumors, 27 (9%) synchronous metastases, and 18 (6%) underwent resection for recurrent pNETs. All patients were treated with curative intent resection of all disease sites. Grade 2 or 3 tumors were present in 79 patients (34%), 86 (29%) had primary tumor size ≥ 4 cm. Median follow-up time was 37 months, and 5-year RFS was 75% [95% CI 68%-81%]. Those with CgA >5x ULN (n=28) had 5-year RFS of 63%, compared to 75% for 1-5x ULN (n=88), and 77% for normal (n=180, p=0.15). Cox regression analysis in the risk score development cohort yielded four variables meeting criteria for inclusion in the risk score: CgA >5x ULN (HR 4.4, p=0.01), tumor grade 2/3 (HR 3.9, p=0.01), resection for recurrent disease (HR 5.9, p<0.01), and tumor size >4 cm (HR 4.5, p=0.1).

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Abstracts

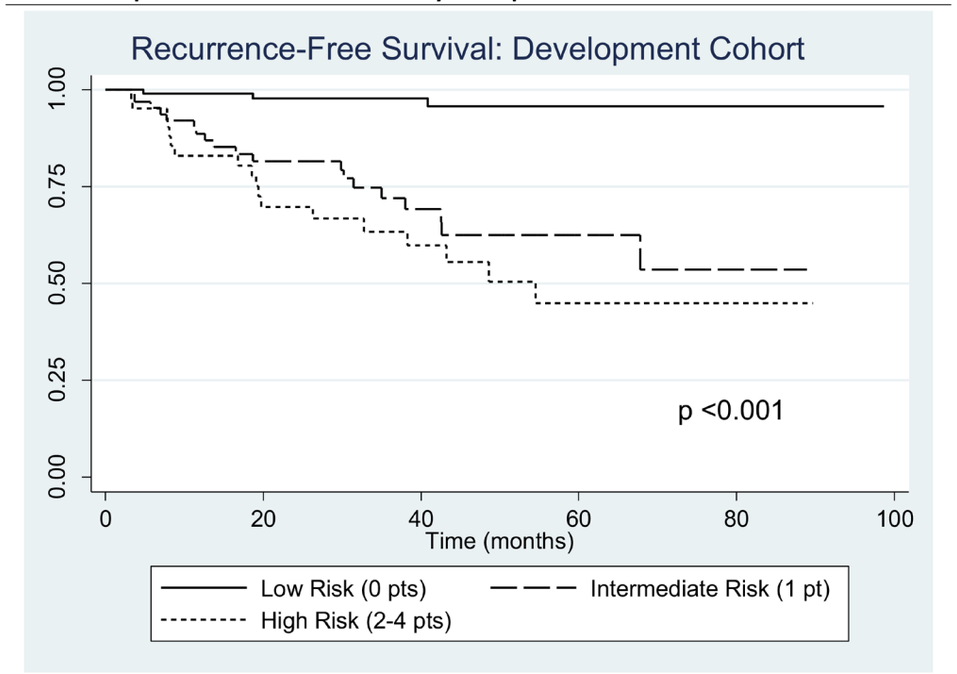
Results *(cont'd)*

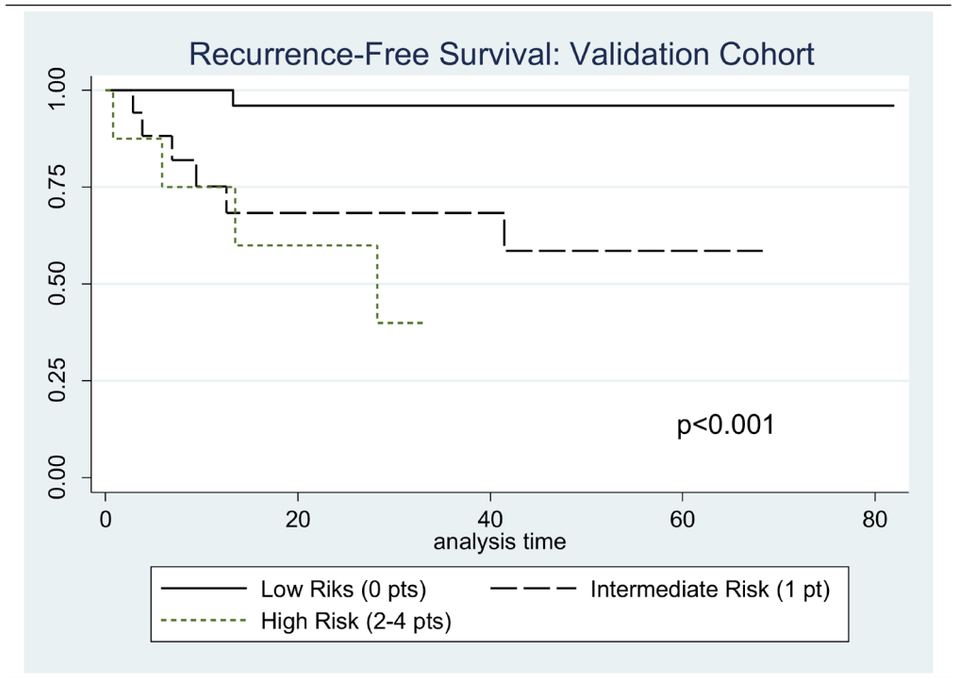
These four variables were assigned 1 point each in the risk score model given significant overlap of 95% CI for HR estimates. Patient stratification into low risk (0 points, n=111, 48%), intermediate risk (1 point, n=73, 31%), and high risk (≥2 points, n=48, 21%) groups resulted in significant survival discrimination between groups in both the development cohort (5-yr RFS for low risk 96%, intermediate 63%, and high risk 45%, p<0.001; Figure) and validation cohort (5-yr RFS for low risk 96%, intermediate 59% and high risk 0%, p<0.001; Figure). Risk-score testing in the unique validation cohort of 64 patients resulted in an area under ROC curve of 0.78 with 92% specificity, 33% sensitivity, NPV of 86%, and PPV of 50%.

Discussion

A simple pre-operative risk scoring system that incorporates CgA level, tumor grade, tumor size, and presence of recurrent tumors resulted in a high degree of specificity for identifying patients at low-risk for tumor recurrence. This test can be utilized preoperatively to aid informed decision making.

FIGURE: Kaplan-Meier Survival Curves by Pre-Operative Risk Score





Risk score calculated by assigning 1 point for each of the following: a) CgA >5x upper limit of normal, b) tumor size ≥4 cm, c) tumor grade 2 or 3, and d) recurrent tumor.

Abstracts

Topical Application of a Dual PI3K/mTOR Inhibitor for the Prevention of Anal Carcinogenesis In Vivo

Brooks L. Rademacher, Louise M. Meske, Kristina A. Matkowskyj, Emily D. LaCount, and Evie H. Carchman

Introduction
Patients with anogenital human papilloma virus (HPV) infection are at high risk of developing squamous cell anal dysplasia that can progress to squamous cell carcinoma of the anal canal (SCCA). We have previously shown that systemic dual PI3K/mTOR inhibition results in decreased SCCA in our HPV mouse model of anal carcinogenesis. Here we sought to investigate the effect of the topical application of a dual PI3K/mTOR inhibitor, BEZ235, to the anus on tumor free survival, histopathology and autophagy.

Methods
K14E6/E7 mice were given no treatment (Control), topical BEZ235 (BEZ), a topical carcinogen DMBA (DMBA), or DMBA plus BEZ for a total of 20 weeks. Mice were assessed weekly for tumor development. At 20 weeks they were euthanized and their anuses examined for histopathologic changes at the anal transition zone (ATZ). Slides of the ATZ were assessed for mTOR and PI3K inhibition by immunohistochemistry (IHC) for pS6 and pAKT expression, respectively. Tissues were also examined for autophagic function via LC3β and p62 expression via immunofluorescence (IF). Tumor free survival analysis was conducted used Kaplan Meier statistics, and all comparisons of mean differences in histopathologic score or protein signal were conducted using one-way ANOVA or independent t-tests.

Results
Regarding tumor free survival, mice receiving DMBA alone survived, on average, 16.9 weeks prior to tumor onset, whereas mice receiving both DMBA and BEZ survived, on average, 19.3 weeks ($P<0.000001$). Histopathological analysis revealed a significant decrease in histological mean score comparing DMBA with DMBA plus BEZ ($P<0.000001$). Comparing DMBA versus DMBA plus BEZ, IHC revealed efficacy of topically applied dual PI3K/mTOR inhibitor, via significant decreases in both pS6 and pAKT ($P<0.001$ for both comparisons). Compared to Control mice, both BEZ and DMBA plus BEZ treated mice had significantly higher LC3β expression, signifying autophagic induction ($P<0.005$ for both comparisons), whereas DMBA, BEZ, and DMBA plus BEZ treated mice had significantly lower p62 expression, signifying increased autophagic function ($P<0.0005$ for all comparisons).

Conclusion
Consistent with systemic delivery of a dual PI3K/mTOR inhibitor, topical application of BEZ235 shows prolonged tumor free survival and decreased anal dysplasia which correlated with autophagic induction. These findings confirm that targeted inhibition of the PI3K/mTOR pathway results in autophagic induction and decreased anal carcinogenesis.

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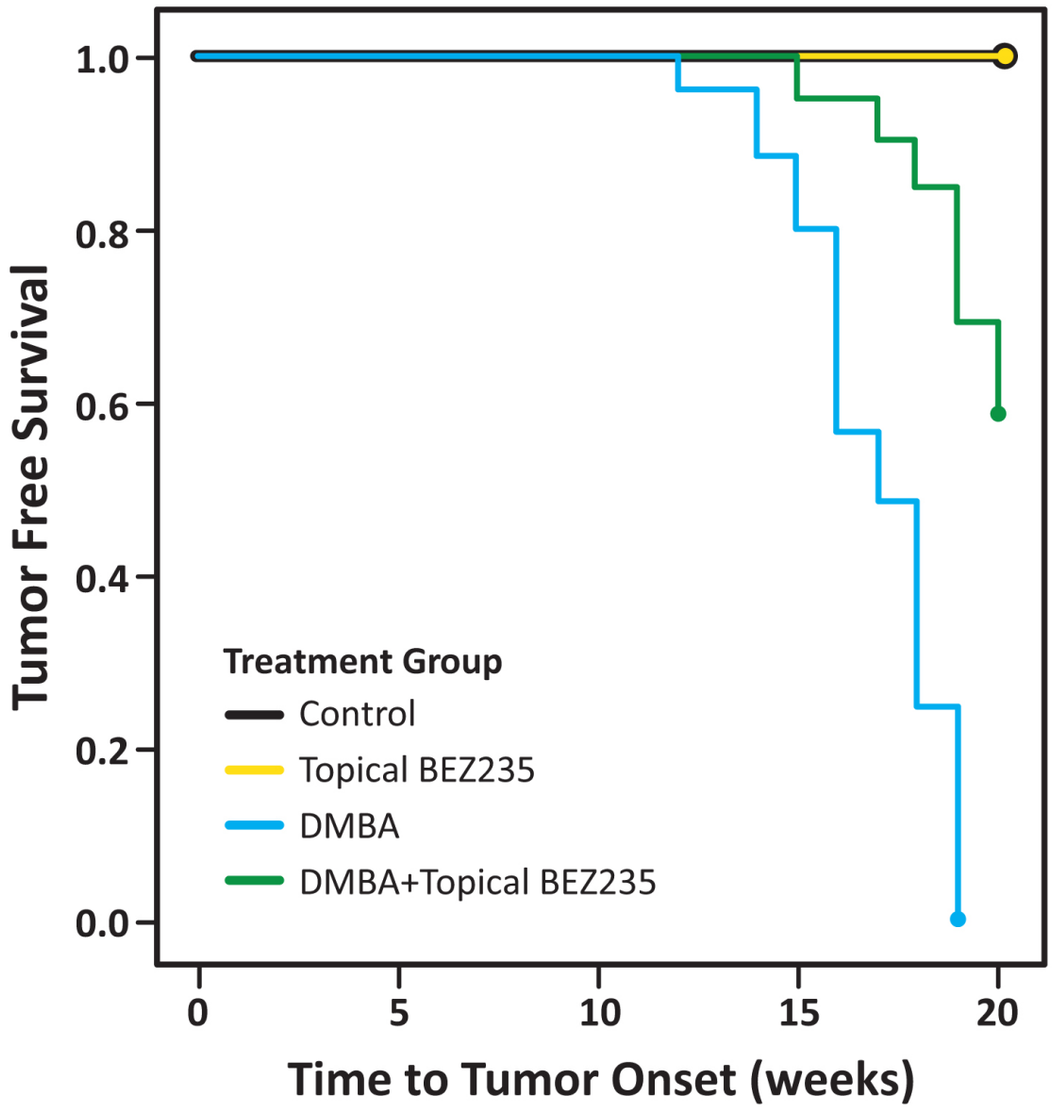
Abstracts


1.0
0.8
0.6
0.4
0.2
0.0
Tumor Free Survival
Treatment Group
Control
Topical BEZ235
DMBA
DMBA+Topical BEZ235
0
5
10
15
20
Time to Tumor Onset (weeks)

Abstracts

BLyS Deficient Rats Prevent Donor Specific Antibody Production and Proliferation in Rodent Model

N Bath, B Verhoven, N Wilson, S Reese, S Panzer, A Djamali, R Redfield

Introduction
Antibody mediated rejection (AMR) is a major cause of kidney allograft failure. APRIL (A proliferation inducing ligand) and BLyS (B Lymphocyte Stimulator) are two critical survival factors for B lymphocytes and plasma cells, the main source of alloantibody. We generated rats deficient in APRIL and BLyS to characterize the effects of targeting these cytokines in our established rodent model of AMR in kidney transplant. Here we report our initial phenotyping and response to alloantigen in these novel rodents.

Methods
Using CRISPR/Cas9 we engineered APRIL-/- and BLyS-/- Lewis rats. The absence of APRIL and BLyS was determined using ELISA and RT-PCR. Spleen, bone marrow, blood, and lymph nodes were also analyzed using flow cytometry, enzyme-linked immunospot (ELISPOT), and immunohistochemistry. APRIL-/- and BLyS-/- rats were sensitized with Brown Norway (BN) blood (complete MHC mismatch). DSA was measured by flow cross match against Brown Norway splenocytes from sensitized wild type (WT), APRIL-/- and BLyS-/- rats. A 3 day mixed lymphocyte reaction (MLR) was performed with splenocytes from BN, Lewis WT, APRIL-/- and BLyS-/- rats to assess cell proliferation.

Results
When challenged with alloantigen, sensitized BLyS-/- had significant decreases in DSA for IgG1, IgG2a, and IgG2b when compared to WT. There was no statistical difference in DSA between APRIL-/- and WT. MLR demonstrated a significant decrease in BLyS-/- cell proliferation when challenged by BN splenocytes compared to APRIL-/- and WT ($p<0.02$). BLyS-/- significantly decreased naïve B lymphocytes (CD45R+IgD+CD24-CD38+CD27+) but preserved transitional B lymphocyte (CD45R+IgD+CD24++) populations when compared to WT and APRIL-/- ($p<0.03$). Additionally, BLyS-/- significantly depleted antibody secreting B cell production of IgM and IgG in all tissues compared to WT and APRIL ($p<0.04$).

Conclusion
BLyS-/- produced fewer alloantibodies and demonstrated a significant reduction in cell proliferation when challenged with alloantigen. Antibody secreting B lymphocytes are also depleted in BLyS-/-, which translates into a reduction of alloantibody production. Alterations in the B cell compartment were also seen in BLyS-/- animals compared to WT and APRIL-/-. Future studies will characterize the effect of BLyS-/- to prevent AMR in a kidney transplant model.

Key Words
alloantibodies, B cells, Tumor necrosis factor (TNF), Rat

Abstracts

Prolongation Of Skin Allograft Survival Through Dietary Supplementation of Ayrl Hydrocarbon Receptor Ligands

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Abstract

The Aryl Hydrocarbon Receptor (AHR) is a cytosolic transcription factor with numerous endogenous and xenobiotic ligands playing a key role in a number of cellular processes especially immune cell function and development. Differential effects of AHR ligands upon CD4 naïve Tcell development has been described with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) inducing regulatory Tcells while FICZ promotes Th17 responses. Prior work demonstrated prolongation of graft survival in a fully mismatched skin allograft model (Balb/c donor to C57BL/6 recipient) with intraperitoneal administration of TCDD and early rejection with FICZ treatment. In the present work we demonstrate prolonged graft survival in a minor mismatch allograft model (C57BL/6 Male to Female) with dietary supplementation with the AHR ligand, Indole-3-Carbinol (I3C). C57BL/6 female mice were maintained on semi-purified base (SPB) diet deficient of AHR-ligands or SPB diet with I3C supplementation (3ppm) for 3wks prior to transplant and for the duration of the model. AHR-mediated graft survival was correlated to decreases in IFNγ producing Graft Infiltrating lymphocytes. Animals maintained on SPB diet demonstrated a loss of intestinal Treg, Innate Lymphoid Cells type 3, and γδ Tcells. However, I3C supplementation led to maintenance of these mucosal immune cell populations as measured by Flow cytometry. Conversely, maintenance of animals on the AHR-deficient SPB diet led to accelerated graft rejection (Median GST of 46 vs 15.5days $p<0.05$). These findings were AHR-dependent as AHR null animals were found to not only reject grafts earlier than WT counterparts but were not responsive to I3C supplementation (Median GST, AHR null on SPB vs I3C diet were 17 vs 15.5 days respectively). Splenocytes isolated from animals on either SPB or I3C diets were collected and cultured in vitro with exposure to HY peptide. ELISA performed on the supernatants demonstrated a decrease in IFNγ and TNFa production in those animals maintained on I3C vs SPB diet. These data suggest dietary AHR ligands mediate prolonged graft survival via blunting Th1 alloreactivity and/or modulating cell trafficking. While the underlying mechanism remains unclear, these data suggest a role for activation of the mucosal immune system via AHR stimulation and dietary AHR ligands play a novel regulatory role in modulating systemic immune responses.

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Multi-scale Structure-Function Relationships in Right Ventricular Failure Due to Pressure Overload

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Abstract

Right ventricular failure (RVF) is the major cause of death in pulmonary hypertension. Recent studies have characterized changes in RV structure in RVF, including hypertrophy, fibrosis and abnormalities in mitochondria. Few if any studies have explored the relationships between these multi-scale structural changes and functional changes in RVF. Pulmonary artery banding (PAB) was used to induce RVF due to pressure overload in male rats. Eight-weeks post-surgery, terminal invasive measurements demonstrated RVF with decreased ejection fraction (70±10% vs 45±15%, Sham vs. PAB, $p<0.005$) and cardiac output (126±40 mL/min vs. 67±32 mL/min, Sham vs. PAB, $p<0.05$). At the organ level, RV hypertrophy was directly correlated with increased contractility, which was insufficient to maintin ventricular-vascular coupling. At the tissue level, there was a 90% increase in fibrosis that had a direct correlation with diastolic dysfunction measured by reduced chamber compliance ($R2=0.43$, $p=0.008$). At the organelle level, transmission electron microscopy demonstrated an abundance of small-sized mitochondria. Increased mitochondria was associated with increased ventricular oxygen consumption and reduced mechanical efficiency ($p<0.05$). These results demonstrate an association between alterations in mitochondria and RV oxygen consumption and mechanical inefficiency in RVF, and a link between fibrosis and in vivo diastolic dysfunction. Overall, this work provides key insights into multi-scale RV remodeling in RVF due to pressure overload.

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Targeted Donor Complement Blockade After Brain-Death Prevents Delayed Graft Function But Not Progression To Antibody-Mediated Rejection In A Non-Human Primate Model Of Kidney Allo-Transplantation

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Abstract

Donor brain death (BD) triggers a complement-mediated inflammatory response that is linked to the pathogenesis of pre-transplant renal injury in deceased donors. Delayed graft function (DGF) is a common complication after renal transplantation and is strongly associated to reduced graft survival and increased rates of antibody-mediated rejection (ABMR). Here, we hypothesized that complement blockade in the brain-dead donor would potentially prevent the progression to DGF and ABMR in the transplant recipient. We evaluated the role of targeted donor management using recombinant human C1 inhibitor (C1-INH) in the prevention of DGF and ABMR. BD was induced and maintained for 20 hours and recovered kidneys were cold-stored for a 44-hour period. They were then transplanted into ABO-compatible, MHC fully mismatched recipients. Donor animals were divided into three groups: G1) Vehicle (n=3 donors, 6 recipients), G2) C1INH 500 U/kg/dose + heparin (n=3 donors, 6 recipients) and G3) Heparin only (n=2 donors, 3 recipients). Animals were followed for a 90-day period and underwent interval biopsies. The main end-points of the study were: 1) Incidence of DGF defined as 10% reduction in creatinine level from the first post-operative day within 1 week of transplant and 2) development of ABMR within 90 days of transplant according to Banff 2013 criteria. Donor treatment with C1-INH showed a protective effect, with none (0/6) of the G2 recipients developing DGF post-operatively. In contrast, 4/6 (66.6%) animals receiving untreated kidneys from G1 donors and 3/3 (100%) from heparin-only treated G3 donors progressed to DGF (p= 0.008). In addition, recipients of G2 kidneys showed a statistically significant reduction in creatinine levels in the first post-operative week compared to G1 and G3 recipients, and renal function normalized to baseline levels by post-operative day 10 ($p < 0.01$). Furthermore, recipients of G2 kidneys expressed markedly reduced urinary NGAL levels, a specific marker of DGF.

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We also observed a significant reduction in the activation of the donor classical pathway of complement as well as a decrease in circulating pro-inflammatory cytokines in G2 donors. All transplanted recipients from donors in G1 (4/4) and G2 (6/6) surviving over two weeks developed ABMR and showed sustained de-novo DSA development post-transplantation. Histopathological findings were consistent with acute active ABMR in the kidney as evidenced by strong C4d staining and peritubular capillaritis and glomerulitis. FACS analysis revealed a higher proportion of class-switched memory B-cells (CD20+, CD27+, IgDlow) in mesenteric and inguinal lymph nodes. We did not observe differences in the incidence or severity of ABMR between animals receiving grafts from either vehicle or C1-INH treated donors. We have generated a unique and reproducible model of DGF and de-novo accelerated ABMR in the rhesus macaque. Our data indicate that donor management targeting complement activation prevented the development of DGF but had no effect on the progression to ABMR in our model. These results suggest a pivotal role for complement activation in BD-induced renal injury and complement blockade as a promising strategy for the prevention of DGF after transplantation.

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Perioperative Outcomes After Extremity Sarcoma Resection - Results of a Contemporary Multi-Institutional Experience

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Introduction
Soft tissue extremity sarcoma (STES) is rare with few multi-institutional experiences contributing to our understanding of perioperative outcomes after resection. Our aim was to identify pre- and intraoperative predictors of perioperative morbidity and mortality after STES resection.

Methods
Patients who underwent resection of STES from 2000-2016 were identified from a retrospective multi-institutional sarcoma database (United States Sarcoma Collaboration). 90-day morbidity and mortality were assessed, based on pre- and intraoperative risk factors, using Chi Squared and Fischer's Exact test. Statistically significant variables ($p \leq 0.05$) were used in multinomial regression analysis to determine independent predictors of morbidity and mortality.

Results
1334 patients underwent primary STES resection with a median age of 57.0 years. The most common histologic subtypes were undifferentiated pleomorphic sarcoma (28.9%), liposarcoma (16.1%), and leiomyosarcoma (8.1%). Overall 90-day morbidity was 22.5% and 90-day mortality was 1.3%. On multivariate analysis, independent predictors of increased 90-day morbidity were age > 65 years (OR=1.57, p=0.003), white v. other race (OR=1.74, p=0.01), obesity (OR=1.74, p=<0.001), lower versus upper extremity (OR=2.22, p<0.001), tumor size > 10 cm (OR=1.80, p<0.001), TNM/FNCLCC grade (OR=1.45, p=0.02), positive nodal status (OR=3.03, p=0.02), R1 v. R0 resection (OR 1.49, p=0.03), and vascular reconstruction (OR=4.52, p<0.001). Independent predictors of increased 90-day mortality on multivariate analysis were age > 65 years (OR=4.59, p=0.01), smoking (OR=5.65, p=0.003), emergency surgery (OR=27.03, p=0.04), tumor size > 10 cm (OR=4.10, p=0.03), and amputation (OR 6.45, p=0.001).

Conclusion
Based on the unique strengths of a multi-institutional collaborative with large numbers of STES patients, we identified factors associated with 90-day morbidity and mortality after resection. These data should guide patient counseling regarding perioperative outcomes in order to better align patient expectation and inform treatment sequencing.

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	90-day Morbidity		90-day Mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age > 65	1.57 (1.17-2.11)	0.003	4.59 (1.44-14.71)	0.010
Race				
White v. Black	0.81 (0.54-1.20)	0.296	-	-
White v. Other	1.74 (1.15-2.64)	0.009	-	-
Obese	1.74 (1.29-2.36)	<0.001	-	-
Smoking	-	-	5.65 (1.81-17.54)	0.003
Emergency Surgery	-	-	27.03 (1.22-500.00)	0.037
Lower v. Upper	2.22 (1.51-3.25)	<0.001	-	-
Size > 10 cm	1.80 (1.36-2.38)	<0.001	4.10 (1.18-14.29)	0.027
Deep v. Superficial	1.30 (0.80-2.10)	0.287	-	-
Grade	1.45 (1.07-1.97)	0.016	-	-
Histology	-	-	3.13 (0.81- 12.04)	0.098
Positive Nodal status	3.03 (1.16-7.88)	0.023	3.31 (0.56-19.61)	0.188
Neoadjuvant Therapy	1.45 (0.98-2.16)	0.066	-	-
Margin				
R1 v. R0	1.49 (1.05-2.11)	0.026	0.97 (0.22-4.30)	0.966
R2 v. R0	1.45 (0.65-3.21)	0.367	<0.00	0.998
Vascular Reconstruction	4.52 (2.15-9.52)	<0.001	-	-
Amputation	-	-	6.45 (2.05-20.28)	0.001

Table 1: Multinomial regression analysis of factors influencing 90-day morbidity and mortality. Factors not significant on univariate analysis denoted with (-). For histology, no subtype was statistically significant in the model. The lowest p-value is shown with its associated odds ratio.

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Natural Language Processing for Thyroid Pathology Reports: Does Synoptic Reporting Improve Information Retrieval?

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Introduction

Pathology results are typically reported in narrative text documents, and synoptic summaries may be used to improve communication of tumor information. Extracting data from text reports requires time-consuming and costly manual review. Alternatively, natural language processing (NLP) systems automatically convert unstructured text to structured, analyzable data. In this study, we describe our methodology and accuracy using NLP to extract tumor characteristics from thyroid pathology reports and specifically analyze how synoptic reporting impacts results.

Methods

First, we iteratively developed NLP tools on thyroid pathology reports using the clinical Text Analysis and Knowledge Extraction System (cTAKES) platform from an academic medical center (site A) and non-academic medical center (site B) from 6/1/2007 – 12/31/2013. We incorporated the following elements in a schema for NLP extraction: date, surgical procedure, diagnosis, tumor laterality, size, measurement units, multifocality, and lymph node metastasis. Next, we evaluated the accuracy of our NLP tools using separate test-sets of pathology reports from the same period at each site. Two physicians independently manually annotated each test-set report. Inter-annotator agreement (IAA) was assessed, and a third physician adjudicated annotation differences. Finally, the gold-standard, manually annotated reference was used to evaluate NLP performance on each test-set.

Results

A total of 183 pathology reports were analyzed from site A (n=161) and site B (n=22), containing 741 relevant data elements. Synoptic tumor summaries were found in 38 reports (23.4%) and 8 reports (36.4%) from site A and B, respectively. IAA was 98.3%. Compared to the gold-standard reference, overall accuracy of the NLP system was 93.7% (site A: 95.6%; site B: 78%). Accuracy for each data element is shown in Table 1. The diagnosis of cancer was recognized when present in all reports. Benign pathology was identified with near perfect accuracy. Most incorrectly retrieved operative procedures (83%) were reported in a non-synoptic narrative. Internally inconsistent reporting of tumor characteristics (e.g. both 'left thyroid' and 'right thyroid' reported in reference to tumor laterality) also accounted for errors.

Conclusions

NLP extracts critical information from thyroid pathology reports with a high level of accuracy. This methodology facilitates high volume, high throughput analysis of thyroid pathology results for clinical and research purposes. In addition, synoptic reporting may improve NLP accuracy in capturing certain data elements.

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Table 1. Accuracy of natural language processing by data element for pathology reports at each institution.

Data element	Site A, No. mentions (% correct)	Site B, No. mentions (% correct)	Both sites, No. mentions (% correct)
Date	161 (100%)	-	161 (100%)
Procedure	161 (97.5%)	22 (91%)	183 (96.7%)
Diagnosis	161 (98.8%)	22 (100%)	183 (98.9%)
Malignant*	56 (100%)	10 (100%)	66 (100%)
Benign	105 (98.1%)	12 (100%)	117 (98.3%)
Tumor laterality	45 (91.1%)	10 (80%)	55 (89.1%)
Tumor size	55 (94.6%)	10 (50%)	65 (87.7%)
Measurement units	55 (92.7%)	10 (50%)	65 (86.2%)
Multifocality	18 (100%)	4 (75%)	22 (95.4%)
Lymph node metastasis	3 (100%)	4 (75%)	7 (85.7%)

*In 2 site A reports and 2 site B reports, the subtype of cancer was partially correct or difficult to interpret.

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A Randomized Controlled Trial Evaluating Receipt of Decision-Aid and Patients' Perception of Information Conveyed During Surgical Consultation

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Introduction
To make an informed decision about breast cancer surgery, it is important for patients to hear about the benefits and risks of all the surgical options. In a prior study, a significant proportion of breast cancer patients (41%) reported that not all surgical options were discussed with them; further, more patients reported discussing breast conserving surgery (BCS) than mastectomy. We hypothesized that providing patients with high quality information prior to the surgical consultation would prepare them for the consultation and increase the likelihood that they would report both options being discussed. The objective was to examine the impact of pre-consult information on patients' perception of information conveyed during their surgical consultation.

Methods
In this randomized control trial, Stage 0-3 breast cancer patients were prospectively randomized to an email link to standard websites (National Cancer Institute, American Cancer Society, Breastcancer.org) versus a decision aid. Patients seeking second opinions, diagnosed by excisional biopsy, or without an email address were ineligible. Patients completed a survey following surgical consultation that assessed perceptions of the information conveyed (n=211). Descriptive statistics were generated and univariate statistics used to compare findings between study arms. Multivariable logistic regression models were used to assess the association between patients' perception of information conveyed and age, education, stage, and surgeon. The change in pseudoR2 estimated the proportion of the variance in patients' perception that was attributable to patient factors, study arm, and surgeon.

Results
The median age was 60 years (range 27-80), 98% were white, 55% had stage I cancer, and 87% had at least some college education; demographics were similar between study arms (p=NS). There was no association between study arm and reported discussions for either BCS or mastectomy. Overall, 94% of patients reported that their surgeon discussed lumpectomy as an option for them versus 76% for mastectomy (Table). 70% reported that their surgeon discussed both options.

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Results *(cont'd)*
The individual surgeon that a patient saw was a strong predictor of patients' perceptions of whether mastectomy was discussed as an option for them (p=0.0001), whether reasons to have a mastectomy were discussed (p=0.004), and whether reasons not to have BCS were discussed (p=0.03). Of the patient factors, only stage was associated with information conveyed, with patients with higher stage cancers more likely to report that their surgeon discussed reasons to have a mastectomy (p=0.01).

Conclusion
Overall, the majority of patients reported hearing about both BCS and mastectomy as options for them. Importantly, this included a balanced discussion around the reasons for and against a given procedure. However, patients were still less likely to describe having mastectomy discussed as an option for them, with surgeon seen explaining most (73%) of this variation. This emphasizes the significant influence of provider discussions in this preference-based decision. Further work will evaluate patient-surgeon communication directly to identify opportunities to intervene.

Table. Patient Perceptions of Information Conveyed During Surgical Consultation

	% (N)
Did any of your health care providers talk about lumpectomy as an option for you?	94%
Did any of your health care providers talk about mastectomy as an option for you?	76%
Did you and your health care providers talk about reasons to have a lumpectomy?	94%
Did you and your health care providers talk about reasons **not** to have a lumpectomy?	69%
Did you and your health care providers talk about reasons to have a mastectomy?	83%
Did you and your health care providers talk about reasons **not** to have a mastectomy?	80%
**As there were no differences between study arms, the data presented represents the overall cohort*	