Abstract Book

Society of Surgical Oncology 65th Annual Cancer Symposium

Orlando, Florida
March 21–24, 2012

Electronic supplement to
Annals of Surgical Oncology
An Oncology Journal for Surgeons

65th ANNUAL
Cancer
SYMPOSIUM

Society of Surgical Oncology

March 21–24, 2012 • Orlando, Florida

Annals of Surgical Oncology
An Oncology Journal for Surgeons

The Official Journal of the Society of Surgical Oncology
The Official Journal of the American Society of Breast Surgeons
An Official Journal of Brazilian Cancer Society, Federacion Latinoamericana de Cirugia, Hellenic Society of Surgical Oncology, Sociedad Mexicana de Oncologia, and Society of Oncology and Cancer Research in Nigeria

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Volume 19, Supplement 1, February 2012

This supplement was not sponsored by outside commercial interests.

Session Titles and Abstracts Contents

ABSTRACTS

Accepted for
PLENARY and PARALLEL SESSIONS

65th Annual Cancer Symposium
Society of Surgical Oncology
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Ann Surg Oncol (2012) 19:S6–S179
DOI 10.1245/s10434-012-2244-3

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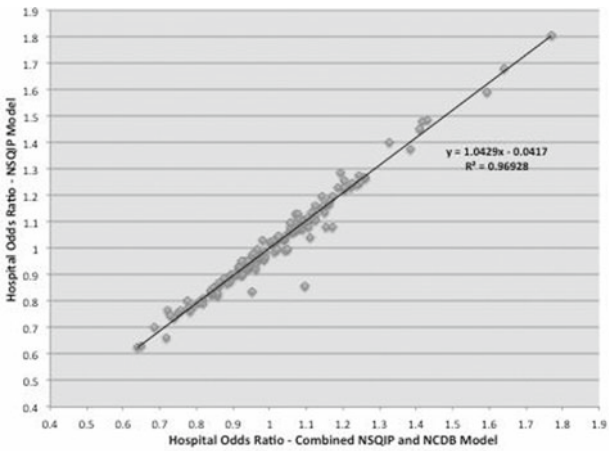
Do Cancer-specific Variables Improve Risk-adjusted Hospital Quality Comparisons? R.P. Merkow,[1]* T.E. Kmiecik,[1] D.J. Bentrem,[1] W.B. Chow,[2] M.E. Cohen,[3] B.L. Hall,[4] C.Y. Ko,[2] K.Y. Bilimoria.[1]
1. Northwestern University Feinberg School of Medicine, Chicago, IL; 2. University of California, Los Angeles and VA Greater Los Angeles Healthcare System, Los Angeles, CA; 3. Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL; 4. Washington University in St Louis and Barnes Jewish Hospital, St. Louis, MO.

INTRODUCTION: For patients undergoing surgery for cancer, it has been suggested that risk-adjustment with cancer-specific variables is needed when evaluating short-term outcomes. Our objectives were to assess the influence of cancer-related variables on postoperative complications and hospital quality comparisons. METHODS: Patients from ACS NSQIP and NCDB who underwent colorectal resection for cancer were linked (2006-2008) to create a dataset containing robust information on comorbidities, complications, and oncologic variables. Three hierarchical models were developed predicting the NSQIP outcome 30-day mortality or any serious morbidity using variables from (1) NSQIP only, (2) NCDB only, and (3) a combined model using NSQIP and NCDB. Models were compared with fit statistics and hospital outlier agreement. RESULTS: From 146 NSQIP hospitals, 11401 patients underwent a colorectal resection for cancer, of which, 1954 (17%) experienced a mortality or serious morbidity event. The first five variables selected in the NCDB-only model were Charlson comorbidity score, neoadjuvant therapy use, T stage, primary payer, and M stage (c-statistic, 0.64; AIC, 9886). The first five variables selected in the NSQIP-only model were ASA class, preop sepsis, albumin, surgical procedure, and COPD (c-statistic, 0.66; AIC, 9787). In the combined model, neoadjuvant therapy use was the only cancer-specific variable selected in the top five. The remaining variables were ASA class, preop sepsis, albumin, and wound class (c-statistic, 0.67; AIC, 9455). At the hospital-level, the NCDB-only model identified three high outliers (worse than expected) and one low outlier (better than expected). Both the NSQIP-only and combined models identified the same four high and two low outlying hospitals (kappa: 1.0) (figure), which agreed marginally with the NCDB-only model (kappa: 0.59). CONCLUSION: Addition of cancer-specific variables to NSQIP models slightly improved model fit; however, hospital outcome comparisons were identical. For patients with colorectal cancer undergoing resection, cancer-related factors have limited predictive ability for short-term outcomes and did not influence hospital quality comparisons.



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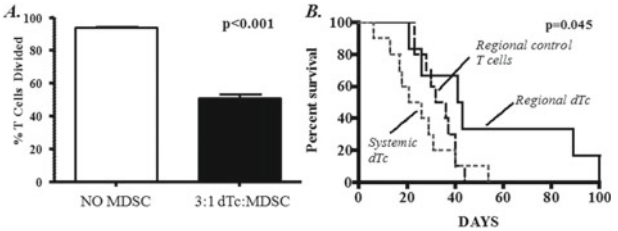
Anti-CEA Designer T-cells are Suppressed by Liver Myeloid Suppressor Cells and Regional Infusion Enhances Efficacy for the Treatment of Intrahepatic Metastases S. Naheed, N. Ahmed, C. Nguyen, A. Bais, Q. Ma, L. Licata, N. Espat, R. Junghans, S. Katz.*
Surgery, Roger Williams Medical Center, Providence, RI.

Introduction: We have ongoing clinical trials for the evaluation of anti-CEA genetically modified or designer T cell (dTc) infusions for patients with CEA+ liver metastases (LM). Using a parallel murine model, we identified a factor suppressing dTc function and a potential strategy for enhancing the efficacy of dTc for LM. **Methods**: Murine splenocytes were transduced with a chimeric antigen receptor (CAR) containing an anti-CEA immunoglobulin moiety (MN14), the CD3ζ chain, and the CD28 co-stimulatory molecule. dTc proliferation was measured by flow cytometry, and myeloid derived suppressor cells (MDSC) were added to test their suppressive capacity. CEA+ colorectal LM were established via splenic injection and dTc were infused via the portal vein or tail vein (PV and TV). **Results**: After injection of $2.5x10^6$ murine colorectal cancer cells (MC38-CEA), we found that MDSC (CD11b+Gr1+) expanded 2.4-fold compared to normal mouse livers. After 7 days of tumor growth, MDSC comprised 72.2% of liver CD45+ cells compared to 30.1% in normal livers (p=0.007). Addition of MDSC to dTc (3:1 responder:suppressor ratio) resulted in a significantly decreased percentage of CD3+ dTc undergoing division (53.1 vs 94.1%, p<0.001, Figure A). MDSC suppressed both CD4+ and CD8+ dTc when analyzed separately (p<0.001). Given the suppressive effects of liver MDSC, we attempted to enhance the delivery of dTc to the site of disease by regional infusion. PV injection of dTc resulted in a 6.7-fold increase in dTc delivery to the liver compared to TV (2.3 vs 0.4% of liver T cells, p=0.05). In mice with LM, PV infusion of anti-CEA dTc led so a significant prolongation of survival (p=0.05, Figure B). **Conclusion**: Growth of LM results in a significant expansion of MDSC that suppressed anti-CEA dTc division. Regional infusion of dTc represents a potential strategy to overcome the suppressive intrahepatic milieu induced by LM growth. **Work supported by the Society of Surgical Oncology Clinical Investigator Award*



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Neoadjuvant Aromatase Inhibitor Therapy Permits Breast Conservation in Postmenopausal Women with Large, Estrogen Receptor (ER)-Rich Breast Cancer Facing Mastectomy: Results from The American College of Surgeons Oncology Group (ACOSOG) Z1031 Trial J.A. Olson,[1]* B.V. Gildy,[2] G. Unzeitig,[3] P.K. Marcom,[1] J.M. Guenther,[4] K. Deshryver,[5] C. Allred,[5] H. Le-Petross,[5] V. Suman,[6] K.K. Hunt,[2] M.J. Ellis.[5] *1. Duke University, Durham, NC; 2. MD Anderson Cancer Center, Houston, TX; 3. Doctors Hospital of Laredo, Laredo, TX; 4. Good Samaritan Hospital, Cincinnati, OH; 5. Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO; 6. Mayo Clinic, Rochester, MN.*

OBJECTIVE: Neoadjuvant aromatase inhibitor (AI) therapy improves surgical options for postmenopausal women with ER - rich breast cancer. A randomized trial in postmenopausal stage II/III ER+ breast cancer was conducted to assess AIs in the neoadjuvant setting with respect to clinical response and breast conservation (BCS) rates. METHODS: 377 patients were randomized to letrozole (2.5 mg/day), anastrozole (1 mg/day), or exemestane (25 mg/day) for 16 weeks. Surgeons reported patients as either marginal for BCS (mBCS), candidate for mastectomy only (cM), or inoperable (I). Stratified logistic regression was used to identify pre-treatment characteristics associated with conversion from cM or I to BCS. RESULTS: Three patients withdrew consent leaving 374 patients for analysis (T2: 74.6%; T3: 19.5%; T4a-c: 5.9% and 71.4% clinically node-negative). At baseline, surgical eligibilities were cM : 45.7%; mBCS: 53.2%; and I: 1.1%. Clinical response (by WHO criteria) across all arms was 69% (258/374). Of 352 patients who underwent surgery after AI, 241 (68.5%) had BCS, including 84 of 163 (51.5%) who were cM or I at baseline. Baseline clinical T stage was associated with increased likelihood of conversion from cM or I to BCS after AI (Likelihood ratio test p value < 0.001). The final decision on surgery was surgeon recommendation in 75% and patient preference in 25%. After AI therapy, 27 of 111 (24.3%) patients undergoing mastectomy had pathological T1 disease suggesting mastectomy was unnecessary. CONCLUSIONS: Neoadjuvant AI allows BCS in a substantial proportion of patients with ER-rich tumors considered candidates for mastectomy.

Better techniques to determine residual tumor burden and a willingness to attempt BCS in patients with responsive tumors could improve the rates of successful BCS after neoadjuvant AI.

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Therapeutic Targeting of SFRP2 is a Strategy to Reduce Triple Negative Breast Tumor Growth E.M. Fontenot,* R. Mumper, X. Shen, S. Siamakpour-Reihani, E.G. Hilliard, B. Bone, D.P. Ketelsen, C. Ross, E.C. Rossi, C. Patterson, N. Kauber-DeMore. *Surgical Oncology, University of North Carolina at Chapel Hill, Durham, NC.*

Background: Secreted frizzled related protein 2 (SFRP2) has previously been thought to be a tumor suppressor by inhibiting beta-catenin activation. However, we found that SFRP2 promotes angiogenesis via activation of NFAT, a transcription factor that stimulates both angiogenesis and tumor growth. We hypothesize that SFRP2 is an oncoprotein rather than a tumor suppressor. In this study we evaluate the effect of SFRP2 on the Wnt pathway in breast tumor and endothelial cells, and the effect of SFRP2 antagonism on breast tumor growth in vivo. Methods: Wnt pathway: MDA-MB-231 and 2H11 endothelial cells were incubated with recombinant SFRP2 (7nM) or control for 1 hour. Cells were lysed, nuclear fractions collected and Western blotting performed probing for NFATc3 and beta-catenin. In vivo efficacy study: MDA-MB-231 human breast cancer xenografts were established in 6-week-old female nude mice. Mice were inoculated with 1 x 106 cells s.c.. Treatment began when average tumor size was 200 mm3. Animals were allocated (n = 12 per group) to buffer control, SFRP2 MAb 4 mg/kg iv twice weekly; or Avastin 5 mg/kg iv twice weekly. Tumors were harvested when tumor diameter reached 2 cm or at 28 days. Tumor volumes were measured with a caliper. Growth rates (percent change per day) were compared with the formula ((Final volume- initial volume)/ initial volume) x 100 / number of days. Differences in growth rate between treated and control were analyzed with a two tailed t-test. Results: Wnt pathway: SFRP2 increased nuclear beta-catenin and nuclear NFATc3 in both breast cancer and endothelial cells. Efficacy in triple negative breast cancer: There was a 41% decrease in growth rate between SFRP2 MAb and control (p=0.03) and a 20% inhibition of growth rate between Avastin and control (p=0.40). An IgG negative control had no effect on tumor growth. Conclusion: SFRP2 activated both beta-catenin and NFATc3 in breast cancer and endothelial cells, suggesting that SFRP2 is not a tumor suppressor. SFRP2 antagonism with a monoclonal antibody resulted in a reduction in breast tumor growth, in a tumor that was not sensitive to Avastin. This suggests that SFRP2 is a therapeutic target for breast cancer.

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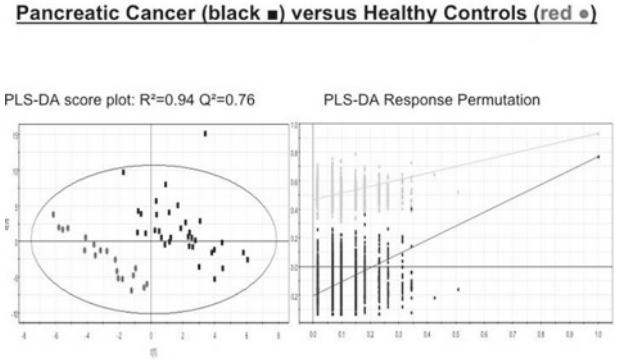
The Metabolomic Signature of Pancreatic Cancer in Urine V.W. Davis,* D.E. Schiller, M.B. Sawyer. *University of Alberta, Edmonton, AB, Canada.*

INTRODUCTION: Pancreatic cancer remains one of the leading causes of cancer-related death, in part owing to the lack of effective means of early detection and screening. Metabolomics, the newest of the "omics" sciences, provides a means for non-invasive screening of early tumor- associated perturbations in cellular metabolism. We applied metabolomic techniques to identify urinary metabolites capable of facilitating in the diagnosis of pancreatic cancer. METHODS: Urine samples from patients with pancreatic cancer (n=55) and healthy volunteers (n=25) were collected and examined using 1H-NMR spectroscopy. Targeted profiling of spectra using Chenomx NMR Suite 7.0 software permitted quantification of 66 metabolites. Unsupervised (PCA) and supervised (PLS-DA) multivariate pattern recognition techniques were applied to discriminate between sample spectra of pancreatic cancer patients and healthy volunteers using SIMCA-P (version 11, Umetrics, Umeå, Sweden). RESULTS: Significant differences were found when comparing the concentrations of 66 metabolites in the urine of healthy volunteers and patients with pancreatic cancer. Those metabolites contributing the most class discriminating information included choline, 2-aminobutyrate, urea and 2-oxoglutarate. Clear distinction between patients with pancreatic cancer and healthy controls was noted when PLS-DA was applied to the data set (see Figure). Model parameters for both the goodness of fit R2, and the predictive capability Q2, were high (R2 = 0.829; Q2 = 0.76). Model validity was tested using response permutation and results were suggestive of excellent predictive power (see Figure). Application of PLS-DA to the data set also revealed clear discrimination of Stage I-III and Stage IV disease states, with the following model parameters, R2 = 0.62; Q2 =0.45. CONCLUSIONS: Urinary metabolomics detected clear differences in the metabolic profiles of patients with pancreatic cancer and healthy volunteers. The early results presented here suggest that metabolomic approaches may facilitate the discovery of novel biomarkers capable of early disease detection.



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WITHDRAWN

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Radioembolization with Yttrium-90 Microspheres is Associated with a Significantly Improved Survival Compared to Conservative Therapy after Treatment of Unresectable Hepatic Tumors: A Large Single Center Experience of 537 Patients A. Saxena,[1]* T.C. Chua,[1] B. Meteling,[2] D.L. Morris,[1] L. Bester.[2] *1. Surgery, St George Hospital, Kogarah, NSW, Australia; 2. St Vincents Hospital, Sydney, NSW, Australia.*

Introduction Several studies have demonstrated the efficacy of yttrium-90 radioembolization in the treatment of both primary and secondary unresectable hepatic malignancies. There is, however, a paucity of literature comparing the outcomes of patients who, after initial evaluation, proceeded with yttrium-90 radioembolization and those who were managed more conservatively. Methods Five-hundred and thirty-seven patients underwent initial evaluation for 90Y radioembolization; of these, 422 patients were suitable for treatment with 90Y radioembolization (Group 1) and the remaining 115 were not (Group 2). The most frequent pathological diagnosis was colorectal cancer (n=287). Patient, pathological and treatment characteristics were compared between the two groups using t-test and chi-square analysis, where appropriate. Survival outcomes were evaluated using the Kaplan-Meier method and compared using the log-rank test. Results The median length of follow-up for all patients after initial evaluation was 11.5 months (range, 2 to 59). Median survival of patients who received 90Y therapy was 10.5 months with a 1- and 3- year survival of 44% and 20%, respectively. Median survival of patients not treated with 90Y radioembolization was 4.0 months with a 1- and 3- year survival of 29% and 15%, respectively. This was statistically significant ($p<0.001$). In patients with colorectal cancer, median survival in patients treated with and without 90Y radioembolization was 11.4 and 6.7 months, respectively ($p=0.003$). In patients with non-colorectal cancer, median survival in patients treated with and without 90Y radioembolization was 9.1 months and 2.5 months, respectively

(p<0.001). Conclusion These data suggest that 90Y radioembolization is associated with a significantly improved survival in patients' referred for an initial evaluation. Whilst confounding factors may play a role, offering this treatment may confer the best prognosis.

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Bayesian Belief Network Model for Peritoneal Mesothelioma after Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Accurately Predicts Survival N.P. Schaub,[1]* M. Alimchandani,[1] M. Quezado,[1] P.M. Kalina,[2] J.S. Eberhardt,[2] H.R. Alexander,[1] D.L. Bartlett,[1] S.K. Libutti,[1] J.F. Pingpank,[1] R.E. Royal,[1] M.S. Hughes,[1] U. Rudloff,[1] U.S. Kammula,[1] G.Q. Phan,[1] A. Stojadinovic,[1] I. Avital.[1] *1. Surgery, National Institutes of Health, Rockville, MD; 2. DecisionQ Corporation, Washington, D.C., DC.*

Purpose: Peritoneal mesothelioma is a rare disease with limited treatment options. Patients are commonly treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Estimation of survival following treatment can guide treatment decisions and impact postoperative surveillance. Currently, no assessment tool exists to estimate survival in mesothelioma patients undergoing CRS and HIPEC. Methods: From 1994 to 2010, 104 patients undergoing CRS and cisplatin-based HIPEC for peritoneal mesothelioma were reviewed. Demographic, laboratory, operative, and histopathological factors were analyzed using statistical software (DecisionQ's FasterAnalytics™). Probabilistic models using machine-learned Bayesian Belief Networks (BBNs) were developed using stepwise training, testing, and cross-validation. Receiver operating characteristic (ROC) curve analysis was conducted. Area under the curve (AUC) and positive predictive value (PPV) for 3- and 5-year overall survival (OS) were calculated. Results: The mean peritoneal cancer index (PCI) was 16, and 66% of patients had a completeness of cytoreduction score equal to zero or 1. Eighty-two percent of patients had epithelial subtype of mesothelioma. The median follow-up time was 33 months (range: 1-192). The 3- and 5-year OS was 56% and 40%, respectively. Three variables with the greatest influence on OS were histological subtype, PCI, and preoperative serum CA-125. Other factors lacked prognostic significance or overlapped these three variables. Cross-validation of the 3-year OS BBN model yielded a mean AUC of 0.77 (95% CI: 0.65-0.89) and PPV of 76%. Cross-validation of the 5-year OS BBN model demonstrated a mean AUC of 0.74 (95% CI: 0.60-0.89) and PPV of 86%. Conclusion: The machine-learned BBN model using histological subtype, PCI, and preoperative CA-125 accurately predicts 3- and 5-year survival in patients undergoing CRS and HIPEC for peritoneal mesothelioma. Estimation of survival may individualize patient treatment and follow-up, such as influencing the extent of systemic therapy and frequency of diagnostic imaging.

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American Joint Committee on Cancer Staging Classification for Pancreatic Neuroendocrine Tumors Does Not Adequately Differentiate Outcomes following Pancreatectomy N.B. Jones,* S.P. Albert, W.L. Frankel, C.R. Schmidt, M. Bloomston. *Surgical Oncology, Ohio State University, Columbus, OH.*

The American Joint Committee on Cancer (AJCC) 7th edition staging manual recently introduced its first TNM staging system for pancreatic neuroendocrine tumors (PNETs) derived from the staging system for exocrine pancreatic adenocarcinomas. We compared this new system to the European Neuroendocrine Tumors Society (ENETS) in patients who underwent surgical resection of a primary PNET. Methods Patients with PNET that were surgically resected at our institution between 1989 and 2008 were assigned a stage (I to IV) based on the new AJCC and ENETS classification. Overall survival was measured from time of resection to date of last follow-up or date of death, and we compared survival between patients in each AJCC or ENET stage. Results We identified 125 patients who underwent resection of PNETs; 43 also underwent multivisceral resection or combined resection of liver metastases. On the basis of histologic grade, 5-year estimated survival rates for low-, intermediate-, and high-grade tumors were 83% (N=99), 38% (N=21), and 40% (N=5) respectively. 5-year OS for ENETS classification of stages I, II, III, and IV were 91% (N=24), 87% (N=38), 65% (N=36), and 52% (N=27), respectively (p<0.001). In contrast, using the AJCC classification, 5-year OS rates for stages I through IV were 91% (N=56), 65% (N=41), N/A (N=1), 52% (N=27), respectively (p<0.001). Only one patient was classified as stage III in the AJCC system. Table 1 compares survival statistics between ENETS and AJCC staging systems. Conclusion In patients with resected PNET, grade, AJCC, and ENET stage are associated with outcomes. The new AJCC staging system fails to differentiate intermediate stages (II &III) as effectively as the ENETS method and therefore does not improve upon prior classifications.

Staging Classification Comparison for Pancreatic Neuroendocrine Tumors

	ENETS Staging				AJCC Staging			
Survival	I	II	III	IV	I	II	III	IV
N	24	38	36	27	56	41	1	27
2-year	100%	90%	86%	67%	95%	85%	N/A	67%
5-year	91%	87%	65%	52%	91%	65%	N/A	52%
10-year	82%	79%	60%	16%	83%	59%	N/A	16%

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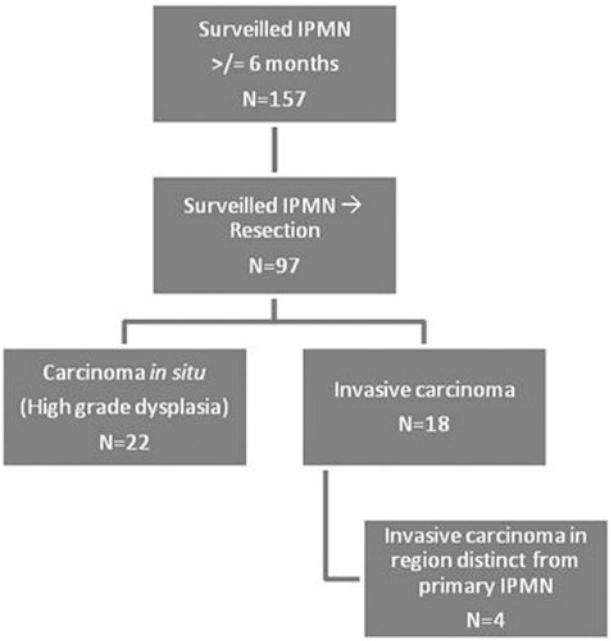
Malignant Progression in Intraductal Papillary Mucinous Neoplasms of the Pancreas: Results of 157 Patients Initially Selected for Radiographic Surveillance J. LaFemina,[1]* S. Gaujoux,[1] T. Kingham,[1] R.P. DeMatteo,[1] Y. Fong,[1] M.I. D'Angelica,[1] W.R. Jarnagin,[1] N. Katabi,[2] R.K. Do,[3] M.F. Brennan,[1] P.J. Allen.[1] *1. Memorial Sloan-Kettering Cancer Center, Department of Surgical Oncology, New York, NY; 2. Memorial Sloan-Kettering Cancer Center, Department of Pathology, New York, NY; 3. Memorial Sloan-Kettering Cancer Center, Department of Radiology, New York, NY.*

Introduction. Natural history studies suggest that intraductal papillary mucinous neoplasm (IPMN) is a field defect of pancreatic ductal instability. The risk of malignancy is well known, but it is unclear if the radiographic abnormality is the predominant site at which this progression occurs. This study analyzes the prevalence and site of pancreatic ductal adenocarcinoma (PDAC) progression in patients initially selected for radiographic surveillance. Methods. Patients evaluated for pancreatic cystic lesions between 1995-2010 were reviewed. Patients were included if they were followed for > six months for a cystic lesion with either a documented cyst fluid CEA >/= 200 ng/mL or pathologic confirmation of an IPMN. Results. Of the 157 patients initially selected for surveillance, 97 (62%) eventually underwent resection. The median length of surveillance prior to operation was 15 mo (range: 6-193 mo). Pathologically confirmed carcinoma in situ (high grade dysplasia, n = 22) or invasive carcinoma (n = 18) was identified in 40 patients. Of the 18 patients who were found to have invasive carcinoma, 10 had main duct IPMN (56%), 5 had branch duct (28%), and 3 had combined (17%). Four of the 18 patients who developed invasive cancer during surveillance (22% of those resected for carcinoma and 3% of those followed) developed PDAC in a region of the gland distinct from the radiographically identified lesion for which surveillance was recommended. Invasive carcinoma was diagnosed a median of 24 mo after the original IPMN diagnosis. During follow-up (median = 8 months from the cancer diagnosis), 1 patient died of disease, 2 are cancer-free, and 1 patient is alive with recurrence. Conclusions. In this study, 11% of patients with IPMN initially selected for surveillance developed invasive disease; 22% of those tumors arose in an area of the gland distinct from the initially identified lesion. Diagnostic and operative strategies for IPMN should consider the cancer risk in the entire gland.



Malignant progression in 157 patients initially selected for radiographic surveillance of IPMN

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Epithelial-mesenchymal Transition (EMT) Molecular Biomarkers in Malignant IPMN G.J. Lahat,* S. Lowenstein, I. Nachmany, M. Ben haim, R. Nakache, I. Santo, M. Inbar, Z. Halperin, J.M. Klausner, N. Lubezky. *surgical oncology, Sourasky Medical Center, Tel Aviv, Israel.*

Introduction: EMT plays a key role in cancer invasion, metastasis, and drug resistance; thus, it is frequently associated with increased tumor aggressiveness and poor prognosis. The miR-200 family have been implicated in EMT negative regulation directly affecting E-cadherin expression. We evaluated EMT involvement in IPMN tumorigenesis and whether selected EMT biomarkers are differentially expressed between low grade and malignant IPMN. Methods: IPMN resected between 1995- 2011 were reviewed by two GI pathologists. Thirty five IPMN samples were included and grouped into low risk (low grade dysplasia, moderate grade dysplasia, n=15) and high risk (high grade dysplasia, n=10; carcinoma, n=10) categories. 846 human miRNAs were profiled and differentially expressed EMT related miRNAs were validated using quantitative RT-PCR; 27 representing normal and IPMN paraffin embeded samples were immunohistochemically stained for E-Cadherin and Vimentin. These were scored by a GI pathologist. Results: Hierarchical clustering demonstrated grouping of two main IPMN sub-groups: low grade vs. high grade IPMN and carcinoma. Twenty four miRNAs were differentially expressed (14 upregulated, 10 downregulated) in high grade IPMN and carcinoma compared to low grade IPMN ($p<0.05$). The expression of several EMT regulatory miRNAs significantly differ between clusters: of them, miR- 200a,c were down regulated (2 fold decrease) in malignant IPMN as compared to low grade IPMN ($p<0.05$), consistent with the known role of the miR-200 family in negatively regulating EMT. These miRNAs were validated using quantitative RT-PCR. E-cadhein expression, which is directly regulated by the miR-200 family was significantly lower in high grade IPMN and carcinoma vs. low grade IPMN ($p<0.05$). On the contrary, vimentin expression was increased in high risk IPMN samples ($p<0.05$). Conclusions: To the best of our knowledge this is the first study reporting EMT features in malignant IPMN. These data indicate that the miR-200 family may play a role in IPMN biology and therefore could be utilized as potential novel biomarkers identifying high risk IPMN patients most likely to benefit from surgery.

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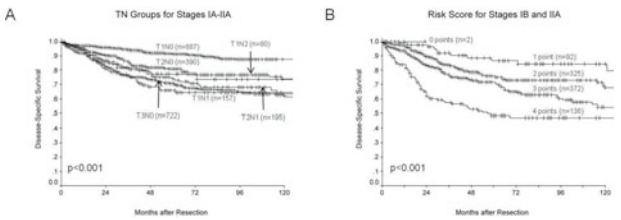
Population-based Outcome of Stages IA-IIA Resected Gastric Adenocarcinoma: Who Should Get Adjuvant Treatment? J.S. Gold,[1]* R.H. Al Natour,[1] M.S. Saund,[2] C.H. Yoon,[2] A.M. Sharma,[1] Q. Huang,[1] V.A. Boosalis,[1] E.E. Whang.[1] *1. VA Boston Healthcare System, West Roxbury, MA; 2. Brigham and Women's Hospital, Boston, MA.*

Introduction: The benefit of adjuvant treatment in gastric adenocarcinoma was demonstrated by randomized controlled studies that predominantly enrolled patients with locally advanced tumors. Thus its role for Stage IIB – IIIC disease is widely accepted. Our aim was to identify patients with Stage IA – IIA gastric adenocarcinoma who have a poor prognosis and therefore may benefit from adjuvant treatment. **Methods:** Patients with local or local-regional gastric adenocarcinoma who underwent surgical resection with pathological evaluation of ≥15 lymph nodes and had available disease-specific survival (DSS) data were identified from the Surveillance Epidemiology and End Results Registry. AJCC 7th edition gastric cancer staging was used. Kaplan-Meier survival was estimated. Survival differences were evaluated with the logrank test and Cox multivariate analysis. **Results:** TN grouping strongly predicted DSS ($p<0.001$, n=8515 patients). Stage IA (T1N0) tumors had a distinctly excellent outcome (panel A), 91±1.2% DSS at 5 years, and thus were excluded from further analysis. The 5 TN groups of Stages IB and IIA had the next best outcomes with DSS ranging from 66±4.6% to 81±2.3% at 5 years (panel A). Older age ($p<0.001$), higher grade ($p=0.004$), larger size ($p<0.001$), and proximal tumor location ($p<0.001$) were independent predictors of worse DSS in Stage IB and IIA tumors. Interestingly, T and N stages did not independently predict outcome ($p=0.07$, $p=0.41$ respectively). We devised a risk stratification scheme for Stage IB and IIA tumors where 1 point was assigned for each of the following variables: age >60 years, tumor size >5 cm, proximal tumor location, and grade other than well differentiated. DSS was 100% at 5 years for patients with no points; 86±4.3% for those with 1 point; 76±3.0%, 2 points; 72±2.8%, 3 points; and 48±4.9%, 4 points (panel B) ($p<0.001$). **Conclusions:** Patients with Stage IB and IIA gastric adenocarcinomas with at least 2 adverse features (age >60 years, tumor size >5 cm, proximal tumor location, and grade other than well differentiated) have 5 year DSS ≤76%. Adjuvant therapy may be warranted for these patients.



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Role of Repeat Staging Laparoscopy in Locoregionally Advanced Gastric Cancer after Completion of Neoadjuvant Therapy K. Cardona,* Q.C. Zou, M. Gönen, V.E. Strong, M.F. Brennan, D.G. Coit. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Staging laparoscopy (SL) can identify occult, subradiographic metastatic disease, either visible or cytologic, defining patients with Stage IV gastric cancer who are unlikely to benefit from gastrectomy. The purpose of this study was to characterize the yield of repeat SL performed immediately prior to gastrectomy following administration of neoadjuvant therapy for locoregionally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. Methods: Retrospective review of a prospective database identified patients with locoregionally advanced G/GEJ adenocarcinoma (T3-4Nany or TanyN+) who underwent pretreatment SL with negative peritoneal cytology followed by neoadjuvant chemotherapy or chemoradiation. After neoadjuvant therapy, patients underwent repeat SL. The yield of repeat SL to identify subradiographic metastatic disease (M1) was determined and outcome data were analyzed. Results: From 1994-2010, 164 patients with locoregionally advanced G/GEJ adenocarcinoma were identified who underwent repeat SL immediately prior to gastrectomy. Occult M1 disease was identified in 12 patients (7.3%). Of these 12 patients, M1 disease was identified at laparoscopy in 9 patients (5.5%)—8 patients had visible disease and 1 patient had positive peritoneal cytology only. M1 disease not identified by SL was discovered at laparotomy in the other 3 patients (1.8%). There were no complications associated with

patients who only underwent SL. Median follow-up was 30 months with a median survival of 18 months for patients with M1 disease and 47 months for patients resected with curative intent without M1 disease (p<0.001). Conclusion: Repeat staging laparoscopy following neoadjuvant therapy for locoregionally advanced G/GEJ adenocarcinoma identifies 5-6% of patients with subradiographic M1 disease. The majority of M1 disease is identified at repeat SL rather than at laparotomy and the majority is visible as opposed to positive cytology only. These patients with occult M1 disease have a poor prognosis, are unlikely to benefit from gastrectomy, and repeat SL can avert the morbidity of a non-therapeutic laparotomy in this patient population.

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Definitive (Chemo) Radiotherapy in Esophageal Cancer Patients: A Population-based Study in North-East Netherlands J. Smit,[1]* C.T. Muijs,[1] G. Paardekooper,[3] P.R. Timmer,[3] K. Muller,[2] D. Woutersen,[4] V.M. Mul,[1] J.C. Beukema,[1] G.A. Hospers,[1] J.A. Langendijk,[1] J.T. Plukker.[1] *1. University Medical Center Groningen, Groningen, Netherlands; 2. Radiotherapeutisch Instituut Stedendriehoek en Omstreken, Deventer, Netherlands; 3. Isala Klinieken, Zwolle, Netherlands; 4. Medisch Spectrum Twente, Enschede, Netherlands.*

INTRODUCTION: Definitive (chemo)radiation as primary treatment modality is offered to esophageal cancer (EC) patients, as an alternative for patients considered medically unfit for surgery or having irresectable tumors. We evaluated the results in our cohort to improve selection of patients for intensified non-surgical strategies and to identify which clinical factors have a prognostic impact on the overall (OS) and disease free survival (DFS). METHODS: EC patients treated with definitive radiotherapy (RT) or chemoradiotherapy (CRT) from 4 radiotherapy referral centers between 1996 and 2008 were used. Only patients with squamouscellcarcinoma (SCC) or adenocarcinoma (AC) were included in the analyses. RESULTS: In total 278 patients were identified of whom 106 (38.1%) were treated with CRT (platinum based, median 50.4 (46.8 – 70)Gy) and 172 (61.9%) with RT alone (median 60 (40-70)Gy). Stage was cT1=5.6%;cT2=15.3%;cT3=60.9% and cT4=18.2%. Nodal stage consisted of cN0=35%;cN1=65%, including cM1a=5.8%. The male/female ratio was 78.3% to 21.7%. AC occurred in 57.6% and 42.4% had a SCC. The overall median age was 69 years. Median OS time was 11 (1-166) months with an OS of 45%, 22% and 6% and a DFS of 32%, 18% and 6% at 1, 2 and 5 years, respectively. There was no significant difference between the CRT and RT group in OS (p=0.09) and DFS (p=0.17). The DFS after 2 and 5 year was 25% and 12% for SCC patients versus 11% and 0% for AC patients (p=0.007). The OS at 2 and 5 year was 28% and 11% for SCC versus 14% and 0% for AC patients (p=0.020). Initial recurrence was seen locoregionally in 66.7% and distant metastases occurred in 33.3%. Common sites for distant recurrence were the liver with 52.4%, 17.5% bones and 15.5% lungs. Patients with SCC had a better response to (chemo)radiotherapy considering the OS (p=0.02, HR=0.7) and DFS (p=0.01, HR=0.69) in a multivariate analysis. CONCLUSIONS: Patients with a SCC esophageal tumor have better long-term results then AC patients after definitive (chemo)radiation. In this patient group SCC seems to be a strong prognostic factor for both OS and DFS. Furthermore the difference between RT and CRT is still small.

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Multimodality Therapy for Borderline Resectable Pancreatic Cancer: A Single Institution Experience J.M. Pimiento,* T. Hutchinson, J. Weber, M. Patel, P.J. Hodul, M.D. Chuong, G. Springett, S.E. Hoffe, R. Karl, B. Centeno, J. Klapman, R. Shridhar, D. Chen, M.P. Malafa. *Surgical Oncology, H Lee Moffitt Cancer Center, Tampa, FL.*

Introduction: Multimodality therapy has been advocated for borderline resectable pancreatic cancer (BRCP); however, specific regimens vary widely by institution. Outcomes of these interventions need to be examined to inform future investigation of the optimal therapy for these patients. This study represents the experience of multimodality therapy for BRPC at an NCI designated cancer center. Methods: We identified all patients (pts) with operable pancreatic ductal adenocarcinoma (PDA) from 2006 to 2011. Patients were divided into two groups: resectable group and BRPC group as per the NCCN and AHPBA consensus guidelines. Primary outcomes were resection rate, microscopic negative margin (R0) resection rate, overall survival (OS), and disease free survival (DFS). Fisher's exact and chi-square were used for group comparison while Kaplan-Meier estimates was used for survival analysis. Results: 160pts were identified with operable PDA. 100 (63%) pts had resectable tumors, and 60 (37%) pts had borderline resectable tumors. Neoadjuvant therapy (NT) was administered to 0% in the group with resectable tumors, and 100% in the group with borderline resectable tumors. The resection rate was 100% in pts with resectable tumors and 58% in pts with borderline resectable tumors. R0 resection rates were 80% in the resectable tumors and 97% in the borderline resectable tumors following NT. Perioperative mortality was <1% (1/125) for resectable tumors and 0% in borderline resectable tumors. Median OS was 22.6 months (m) for pts that had resectable tumors and 13.9m for all pts with borderline resectable tumors (p=0.017); however, the median OS for resected pts with borderline resectable tumors was 21.5m (p=0.6). Improved DFS was seen in patients with resectable tumors when compared with resected borderline resectable tumors (15 vs. 9.5m; p=0.04). Conclusion: Multimodality therapy leads to high rates of R0 resections in borderline resectable pancreatic cancer; however 42% of patients progressed during NT. The overall survival for patients with resected borderline resectable pancreatic cancer following NT is similar to patients who undergo resection for resectable pancreatic cancer.

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The Impact of Vascular Reconstruction on Early Postoperative Outcomes after Pancreaticoduodenectomy: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program Database A.W. Castleberry,[1]* R.R. White,[1] S.G. De la Fuente,[2] D.S. Tyler,[1] T.N. Pappas,[1] J.E. Scarborough.[1] *1. Duke University Medical Center, Durham, NC; 2. Moffitt Cancer Center, Tampa, FL.*

Introduction: Several single-center reports have been published suggesting that vascular reconstruction (VR) during pancreaticoduodenectomy (PD) allows an acceptable oncologic outcome in patients with pancreatic adenocarcinoma without affecting early postoperative mortality or morbidity. The objective of our study was to review the outcomes associated with VR during PD using a large multicenter data source. Methods: A retrospective cohort analysis was performed using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Participant User Files for 2005-2009. All patients undergoing PD for a postoperative diagnosis of malignant neoplasm of the pancreas were included. Forward stepwise multivariate regression analysis was used to determine the association between VR during PD and 30-day postoperative mortality and morbidity after adjusting for patient demographics and comorbidities. Results: 3582 patients were included for analysis, 281 (7.8%) of whom underwent VR during PD. VR during PD was associated with significantly greater risk-adjusted 30-day postoperative mortality (5.7% with VR vs. 2.9% without VR, Adjusted Odds Ratio (AOR) 2.1, 95% CI 1.22-3.73, p = 0.008) and overall morbidity (39.9% with VR vs. 33.3% without VR, AOR 1.36, 95% CI 1.05-1.75, p = 0.02). Patients undergoing VR required significantly longer operative times, and were more likely to require intraoperative transfusion or early reoperation, than patients not undergoing VR during PD. There was no significant difference in risk-adjusted postoperative mortality or morbidity between those patients undergoing VR by the primary surgical team versus those patients undergoing VR by a vascular surgical team. Conclusion: Contrary to the findings of several previously published single-center analyses, data from ACS-NSQIP suggests that VR significantly increases the risk of 30-day postoperative death or complications after PD. Patients who may require VR during PD will likely benefit from referral to centers with sufficient experience with this procedure.

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Partial versus Sleeve Portal Vein Resection in Pancreaticoduodenectomy for Pancreas Cancer: Morbidity Does Not Trump Margins P.T. Kim,* A. Wei, S.M. Black, D. Cavallucci, S. Gallinger, I.M. McGilvray. *HPB Surgery, University of Toronto, Toronto, ON, Canada.*

Introduction: Portal vein (PV) resection during pancreaticoduodenectomy (PD) for pancreas cancer can be performed if the oncologic margin is at stake. Partial portal vein resection in general is deemed safer than sleeve (circumferential) resection. However, partial portal vein resection may not be as thorough as sleeve resection from the oncologic margin standpoint. To address this issue, we compared outcomes between partial and sleeve resections in a large PD series. Methods: A retrospective review of the patients who underwent PD with PV resections from 2000 to 2010 was performed. Results: Over ten years, 654 patients underwent PD. A total of 84 PV resections were per-

formed: 37 partial, 47 sleeve. In the latter group, 8 required venous conduits for reconstruction, 4 required arterial resection and 8 required a right hemicolectomy. The mean age was 63+11 years and pancreatic adenocarcinoma was the most frequent indication (n=67, 80%). Sleeve resection was associated with greater intraoperative blood loss (861+490 vs. 1183+1300cc, p<0.02), higher rate of post operative hemorrhage (19% vs. 2.7%, p<0.01), and increased major Clavien-Dindo complications (IIIa or IIIb), (21% vs. 3%, p<0.02). There was no difference in pancreatic leak (0% vs. 4.3%, p<0.2), delayed gastric emptying (8.1% vs. 6.4%, p<0.7), and there was no post operative mortality. In the 67 patients with pancreas adenocarcinoma, sleeve resections were performed for larger tumors (3.7 + 1.3 vs. 2.8 + 1 cm, p<0.004) but there was no difference in other tumor characteristics (grade, lymphatic, vascular and perineural invasion). When compared to partial PV resection, sleeve resections were associated with a significantly lower rate of positive margins (12.5% vs. 44%, P<0.003). Conclusions: Partial PV resection for pancreas cancer is less morbid than sleeve resection, though both can be done safely with minimal postoperative mortality. However, partial PV resection has a tendency to compromise the surgical margin. Given that a positive margin is generally associated with improved survival, partial PV resection should probably be avoided.

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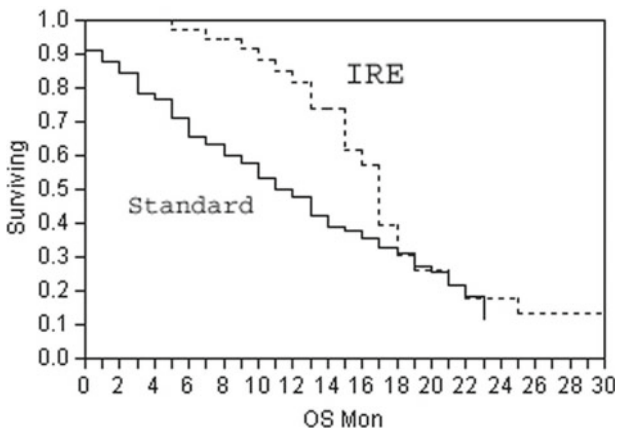
Image Guided Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Improved Overall Survival R.C. Martin,[1]* D. Hayes,[3] W. Goodwin,[3] K. McFarlin,[2] M. Prasad,[2] V. Velanovich.[2] *1. Surgery, Division of Surgical Oncology, Univ Louisville, Louisville, KY; 2. Henry Ford Hospital, Detroit, MI; 3. Baptist Helath, Little Rock, AR.*

Background: Locally advanced unresectable pancreatic adenocarcinoma(LAC) is characterized by poor survival despite chemotherapy and conventional radiation therapy. We have recently reported on the safety of the use of irreversible electroporation(IRE) in the management of LAC. The aim of this study was to evaluate the overall survival in patients with LAC treated with IRE. Methods: A prospective multi-institutional evaluation of 44 patients undergoing IRE for unresectable pancreatic cancer 12/2009 to 10/2010 were evaluated for overall survival and compared to 85 matched stage III patients treated with standard therapy defined as chemotherapy and radiation therapy alone. Results: A total of 44 LAC pts have successfully undergone IRE, with 21 women, 21 men, median age of 61(45 – 80 years). Twenty-nine patients had pancreatic head primary and 15 with body tumors, with 12 pts undergoing margin accentuation with IRE and 32 undergoing in-situ IRE. 40(90%) had pre-IRE chemotherapy alone or chemo-radiation therapy for a median duration 5 months. 32(73%) pts underwent post-IRE chemotherapy or chemoradiation. The 90 day mortality in the IRE patients was 1(2%). In a comparison of IRE patients to standard therapy we have seen a significant improvement in Local progression free survival (14 vs 6 months, P=0.01), Distant progression free survival (15 vs 9 months, p=0.02), and overall survival (20 vs 13 months, p=0.03). Conclusion: IRE ablation of locally advanced pancreatic tumors remians safe and in the appropriate patient who has undergone standard neo-adjuvant therapy for a minimum of 4 months can achieve greater local palliation and improved overall survival when compared to standard chemoradiation-chemotherapy treatments. Validation of these early results will need to be validated in the current multi-institutional Phase 2 IDE study (G110102).



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Effect of MRI on the Management of Ductal Carcinoma In Situ (DCIS) of the Breast M. Pilewskie,* C. Kennedy, C. McGathey, I.B. Helenowski, K. Bethke, N. Hansen, J. Jeruss, S.A. Khan. *General Surgery, Northwestern University, Chicago, IL.*

Introduction: Breast magnetic resonance imaging (MRI) is proposed to be more accurate than mammography in identifying the size and extent of DCIS. The clinical benefit of adding MRI evaluation to pre-operative assessment of DCIS patients to establish the extent of disease and improve surgical planning is debated. There have been mixed reports in small studies of the utility of MRI in changing clinical management and decreasing the rate of re-operation in patients with DCIS. Methods: A prospectively maintained database was reviewed to identify women with DCIS. The rates of additional biopsies, changes in surgical management, and re-operation rates were compared in women with DCIS who underwent pre-operative MRI to those who did not. In addition, the accuracy of MRI assessment of DCIS size was compared to mammogram and pathology size. Results: 355 women were identified with DCIS on core biopsy, 205 of whom underwent pre-operative MRI, 52% obtained prior to surgical consultation. There was no difference noted in the type of initial operation (mastectomy 33.7 % vs 30.0%, p=0.49) or the number of re-operations between the two groups (p=0.10). There was a significant difference in the number of biopsies performed: 92% of women with no pre-operative MRI underwent 1 biopsy, while in the women who had an MRI, 68% had 1 biopsy, 29% had 2 biopsies, and 3% had 3 biopsies (p<0.01). Among women with more than one biopsy, the fraction with additional foci of cancer identified was 37% in the MRI group and 54% in the mammography group (p=0.36). The accuracy of MRI in detecting size of DCIS lesions was inferior to mammogram, regardless of the menopausal status or breast density. The median difference in ratio of imaging to pathology size was: 1.4 (range -3.1 to 8.5) for MRI abnormal enhancement, -0.8 (range -9.2 to 3.0) for MRI mass lesion, and 0.5 (range -6.5 to 10.3) for mammography (p = 0.03 and p<0.01). Conclusion: Among 355 patients with DCIS, the only difference noted in the clinical course with the addition of a pre-operative MRI was the number of biopsies obtained. Our results show no benefit in patients with DCIS undergoing routine pre-operative MRI.

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Factors Associated with Breast MRI Use: A Population-based Analysis B.K. Killelea,* D.R. Lannin, L. Horvath, A.B. Chagpar. *Surgery, Yale University School of Medicine, New Haven, CT.*

Introduction: Although controversial, the use of breast MRI is widespread. We sought to determine patient factors that influenced the use of this imaging modality in a population-based sample. Methods: The National Health Interview Survey (NHIS) is conducted annually by the Centers for Disease Control and is designed to be representative of the American population. The 2010 NHIS data were queried for the use of breast MRI, sociodemographic and risk characteristics. Results: Of the 12,320 women over the age of 30 who were surveyed, 545 (4.4%) reported ever having had a breast MRI. Of these, 138 (32.7%) were done following an abnormal mammogram, 135 (24.8%) for a "breast problem", and 127 (23.3%) as part of a "routine exam". 25 (4.6%) were done due to a family history of breast cancer and 24 (4.4%) because patients were told they were at "high risk". 8 (1.5%) women had a breast MRI because they "requested it". On univariate analysis, factors correlating with MRI use included age (p<0.001), race (p=0.029), insurance status (p<0.001), personal or family history of breast cancer (p<0.001, respectively), benign breast biopsy (p<0.001), and perceived risk of developing breast cancer (p<0.001). Educational status (p=0.962) and region of residence (p=0.190) were not significant. On multivariate analysis, race (p=0.001), personal history (p<0.001), history of benign breast biopsy (p<0.0001), and perceived risk (p<0.001) remained independently associated with MRI use; insurance status (p=0.716), family history (p=0.911) and age (p=0.215) were no longer significant. Among individuals who never developed breast cancer (i.e., a screening population), the only factor associated with the use of MRI was race (p=0.033). Conclusion: Nearly a third of breast MRIs are ordered following an abnormal mammogram, and fewer than 5% are done due to a family history of breast cancer. Factors correlating with MRI use include race, personal history of breast cancer, history

of benign breast biopsy, and patients' perceived risk. Of those without a history of breast cancer (i.e., a screening population), MRI use was correlated only with race, not with actual or perceived risk of developing breast cancer.

Factor	Univariate Analysis		Multivariate Analysis	
	N (%)	p-value	OR (95% CI)	p-value
Age	38 (1.5%)	<0.001	Reference	0.215
< 40 years	101 (4.3%)		1.26 (0.77-2.08)	
40 -49 years	150 (6.2%)		1.66 (1.04-2.67)	
50-59 years	117 (6.2%)		1.38 (0.82-2.33)	
60-69 years	87 (6.3%)		1.41 (0.70-2.86)	
70-79 years	52 (5.8%)		1.11 (0.53-2.30)	
≥ 80 years				
Race	388 (4.5%)	0.029	Reference	0.001
White	127 (6.6%)		1.87 (1.37-2.53)	
Black	24 (3.3%)		0.94 (0.54-1.64)	
Asian	6 (5.0%)		1.16 (0.31-4.34)	
Other				
Insurance status	52 (3.1%)	<0.001	Reference	0.716
Not covered	206 (6.1%)		1.06 (0.63-1.79)	
Medicare	24 (3.0%)		0.79 (0.44-1.41)	
Medicaid	9 (5.1%)		0.82 (0.37-1.78)	
Military	240 (4.7%)		1.08 (0.37-1.60)	
Private				
Personal history of breast cancer	417 (3.8%)	<0.001	Reference	<0.001
No	128 (33.1%)		6.03 (4.28-8.48)	
Yes				
History of benign breast biopsy	304 (4.3%)	<0.001	Reference	<0.001
No	194 (11.9%)		2.21 (1.70-2.87)	
Yes				
First degree relative with breast cancer	455 (4.3%)	<0.001	Reference	0.911
No	90 (7.7%)		0.98 (0.71-1.36)	
Yes				
Perceived risk	154 (11.7%)	<0.001	1.88 (1.35-2.60)	<0.001
High	184 (3.3%)		0.74 (0.55-0.98)	
Average	187 (4.4%)		Reference	
Low				

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Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype R. Ellsworth,[1]* R. Van Laar,[2] B. Deyarmin,[3] C. Shriver.[4] *1. Henry M. Jackson Foundation for the Advancement of Military Medicine, Windber, PA; 2. ChipDx, New York, NY; 3. Windber Research Institute, Windber, PA; 4. Walter Reed Army Medical Center, Washington, DC.*

Background: Determination of ER, PR and HER2 status are standard for predicting prognosis and determining treatment options for patients with breast cancer. In 2010, the American Society of Clinical Oncology (ASCO) and College of the American Pathologists (CAP) issued guidelines for scoring ER and PR status: the cutoff for defining ER/PR positive tumors was defined as >1% positively staining cells and endocrine therapy should be considered for these patients. Here, we determined how this cutoff relates to molecular subtype. Methods: Gene expression data was generated for 258 primary breast tumors from women enrolled in the Clinical Breast Care Project and intrinsic subtype determined using the nearest centroid method (ChipDx LLC). Surrogate IHC-based subtypes were defined as luminal A = ER and or PR+/HER2-; luminal B = ER and or/PR+/HER2+; HER2-enriched = ER and PR-/HER2+ and triple negative = ER, PR and HER2-. IHC-defined subtypes using the new ASCO/CAP definitions of positive ER status were compared to molecular subtypes. Results: The percent of positive staining cells for ER was available for 91% of tumors. Of the tumors with 0% ER staining, 69/70 (98.5%) were either basal-like or HER2-enriched. Of the 10 tumors with ER staining of 1-5%, seven were basal-like and three HER2-enriched. Within the group of 13 tumors with ER staining of 6-50%, those tumors characterized as basal-like had ER values 7-20%, HER2 enriched tumors had ER values 15-46% and luminal A tumors had ER values >20%. Conclusions: Under the new ASCO/CAP guidelines, the 23 tumors assayed here with ER staining between 1-50% would be classified as ER positive, yet 83% are basal-like or HER2-enriched at the molecular level. While it is possible that patients with a small minority of ER positive cells would derive benefit from endocrine treatment, classification of these tumors as ER positive by IHC may preclude the use of PARP inhibitors in those patients with molecularly-defined basal-like breast tumors. Thus, as ER status is a critical element in the choice of treatments for patients with breast cancer, it is imperative that the most effective method for classifying tumors be developed.

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Androgen Receptor-Positive Triple Negative Breast Cancer: A Unique Breast Cancer Subtype L.J. McGhan,[1]* A.E. McCullough,[1] C.A. Protheroe,[1] A.C. Dueck,[1] J.J. Lee,[1] R. Nunez,[1] E.P. Castle,[1] R.J. Gray,[1] N. Wasif,[1] M.P. Goetz,[2] J.R. Hawse,[2] T.J. Henry,[1] M.T. Barrett,[3] C.E. Heather,[3] B.A. Pockaj.[1] *1. Mayo Clinic in Arizona, Phoenix, AZ; 2. Mayo Clinic in Rochester, Rochester, MN; 3. The Translational Genomics Research Institute, Phoenix, AZ.*

Introduction: The role of the androgen receptor (AR) and its expression in triple-negative breast cancer (TNBC) is unclear. Although few studies have evaluated AR expression in TNBC, results have been variable and inconsistent. Methods: A tissue microarray containing a total of 409 tissue cores from 119 patients was stained for the AR, using a previously validated antibody. Tissues stained included TNBC, normal breast tissue, DCIS, lymph node (LN) and distant metastases, and tumor recurrences. Positive AR expression was defined as at least 10% nuclear staining. Results: Epithelial tissue was present and evaluable in 94 TNBC patients with a total of 177 tissue cores. AR expression in TNBC was 22/94 (23%). AR expression in normal breast tissue was 88%, identical to estrogen receptor expression in the same group. AR expression was 73% in adjacent DCIS overall, 100% in DCIS from AR+ TNBC and 55% in DCIS from AR- TNBC. All LN metastases from AR+ TNBC patients were also AR+; conversely no AR- TNBC patient had AR+ LN's. Recurrent TNBC had similar AR expression to the primary tumor. AR expression was associated with older patient age (63 vs. 57 yrs respectively, p=0.051), and LN metastases (p=0.033), table 1. There was also a trend toward higher tumor stage with AR expression, but no difference in tumor size, angiolymphatic invasion or clinical presentation. All patients (4) with a BRCA mutation were AR-. Loco-regional recurrence and overall/disease-specific survival were similar between AR+ and AR- patients, although AR+ patients had more advanced disease. On multivariate analysis the presence of LN metastases was the only significant factor associated with recurrence-free survival (HR 4.34; CI 1.14-16.5). Conclusions: The AR is expressed in normal breast tissue, and expression decreases with advancement to DCIS and invasive cancer. AR+ TNBC was more common in older patients and had a higher propensity for LN metastases. The unique clinical behavior of AR+ TNBC suggests that these patients may benefit from alternative therapeutic interventions such as anti-androgen therapy. Larger studies are required to validate these results.

	AR Negative (N=72)	AR Positive (N=22)	Total (N=94)	p value
Age				0.0511
Mean (SD)	56.6 (13.74)	63.0 (12.09)	58.1 (13.59)	
Body mass index				0.3782
Mean (SD)	27.5 (4.70)	26.4 (5.54)	27.2 (4.90)	
Histology				0.7903
Primary IDC	63 (87.5%)	18 (81.8%)	81 (86.2%)	
Mixed IDC/ILC	2 (2.8%)	1 (4.5%)	3 (3.2%)	
Other	7 (9.7%)	3 (13.6%)	10 (10.6%)	
Tumor grade				0.1040
1	1 (1.4%)	2 (9.1%)	3 (3.2%)	
2	10 (13.9%)	5 (22.7%)	15 (16%)	
3	61 (84.7%)	15 (68.2%)	76 (80.9%)	
Angiolymphatic invasion				0.4323
Yes	14 (19.4%)	6 (27.3%)	20 (21.3%)	
Stage				0.0674
I	40 (55.6%)	6 (27.3%)	46 (48.9%)	
II	24 (33.3%)	12 (54.5%)	36 (38.3%)	
III	8 (11.1%)	4 (18.2%)	12 (12.8%)	
Tumor size (cm)				0.1076
Mean (SD)	2.2 (1.75)	2.9 (1.95)	2.4 (1.81)	
LN metastases				0.0330
Yes	16 (22.2%)	10 (45.5%)	26 (27.7%)	
Presentation				0.4475
Palpable	42 (59.2%)	15 (68.2%)	57 (61.3%)	
Follow-up time (years)				
Mean (SD)	2.9 (2.31)	3.9 (2.62)	3.2 (2.41)	

AR (Androgen receptor); IDC (Infiltrating ductal carcinoma); ILC (Infiltrating lobular carcinoma)

Table: Clinicopathologic factors associated with AR expression in TNBC

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Advanced Imaging Modalities in Early Stage Breast Cancer: Preoperative Use in the United States Medicare Patient M.L. Crivello,[1]* K. Ruth,[2] E.R. Sigurdson,[1] B.L. Egleston,[2] Y. Wong,[3] M. Boraas,[1] R.J. Bleicher.[1] *1. Dept of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. Dept of Biostatistics, Fox Chase Cancer Center, Philadelphia, PA; 3. Dept of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Imaging evaluation of breast cancer has evolved greatly. Guidelines for the use of imaging exist, but adherence remains unknown in the United States. This study was performed to evaluate patterns of imaging in early stage breast cancer usually reserved for advanced stage disease. Meth-

ods: Surveillance Epidemiology and End Results data linked to Medicare claims from 1992 to 2005 were reviewed for stage I/II patients having invasive breast cancer. Claims were searched for patterns of CT scans, PET scans, bone scans, and brain MRIs ("advanced imaging") in the preoperative interval. Results: Among 72,586 patients, 14,105 (19.4%) underwent advanced imaging in the preoperative interval, among whom 90.3% (n=12,740) had stage I/II breast cancer. The proportion of these patients having CTs, PET scans and brain MRIs respectively increased from 5.7% to 12.4% (trend $p<0.0001$), 0.8% to 3.4% (trend $p=0.08$) and 0.2% to 1.1% ($p<0.0001$ trend), between 1992 and 2005. Bone scans declined from 20.1% in 1992 to 10.7% in 2005 (trend $p<0.0001$). For studies having only one diagnosis code, "breast cancer" (174.x) was the only code associated with 76.7% of PET scans, 61.3% of bone scans, 41.6% of CT scans, and 8.9% of brain MRIs. Among the top 30 diagnosis codes per modality, one or more symptoms or metastatic sites was suggested for only 49.1% of brain MRIs, 30.4% of bone scans, 28.6% of CTs, and 12.3% of PET scans. Factors associated with ($p<0.05$) use of all four types of advanced imaging were urban setting, lobular histology, and use of preoperative breast MRI. In the preoperative period, breast MRI was the strongest predictor ($p<0.0001$) of bone scan (OR 1.63, 95% CI 1.44-1.86), CT (OR 2.42, 95% CI 2.12-2.76), and PET usage (OR 5.71, 95% CI 4.52-7.22), when compared with mammography or ultrasound. Conclusion: Aside from bone scans, advanced imaging is increasingly being performed on early stage Medicare breast cancer patients, with limited rationale provided by their coded diagnoses. In light of existing guidelines and increasing scrutiny about healthcare costs, greater education about indications for advanced imaging may be required.

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Role of Axillary Ultrasound (US) in Era of ACOSOG Z0011 and Possible Avoidance of Axillary Lymph Node Dissection (ALND) for Sentinel Lymph Node (SLN)-Positive Breast Cancer (BC) J. Bensenhaver,* A. Nees, T. Breslin, V. Cimmino, A. Chang, M. Sabel, K. Diehl, L. Newman. *Department of Surgery, Division of Surgical Oncology, University of Michigan Health Systems, Ann Arbor, MI.*

INTRODUCTION: Recently reported results from the ACOSOG Z0011 trial have generated enthusiasm for the option of avoiding ALND in breast conserving surgery pts that have SLN metastases. Uncertainty exists regarding whether the ACOSOG results should be generalized to all lumpectomy pts, because of the preponderance of biologically favorable characteristics in the Z0011 participants (majority ER-positive, non-high-grade T1 tumors) and how to manage cases of axillary metastases identified by preoperative US and fine needle aspiration (FNA) biopsy. Our goal was to evaluate the primary clinicopathologic features of FNA-positive BC in comparison with the ACOSOG Z0011 population. METHODS: 240 pts in our single-institution IRB-approved database underwent baseline axillary US with US-guided FNA of morphologically abnormal-appearing LN 2007-2010. Our routine during this timeframe was to perform definitive axillary staging for FNA-negative cases by SLN biopsy and to perform ALND for FNA-positive cases. RESULTS: 116 cases were FNA-negative and follow-up SLN biopsy revealed false negative FNA rate of 24%. Of the 121 FNA-positive cases, 38(31.4%) were T1 lesions and 65(53.7%) were T2. Neoadjuvant CTX was delivered to 40(61.5%) of the T2 tumors and 16(24.6%) of the T2 cases underwent mastectomy because of tumor multiplicity or hereditary risk. Of the T1 lumpectomy tumors, 75% were ER-positive and 62.5% were non-high-grade (similar to the ACOSOG Z0011 population). Notably, all of the T1/FNA-positive cases had less than or equal to two abnormal-appearing lymphnode on axillary ultrasound. CONCLUSIONS: Our results indicate that axillary US should be deferred in favor of proceeding directly to SLN biopsy in T1 potential lumpectomy cases so that these pts can be considered for avoidance of the ALND regardless of nodal status. In T2 BC, axillary FNA remains a valuable strategy for triaging patients that may benefit from neoadjuvant chemotherapy.

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WITHDRAWN

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Prognostic Value of DTCs and CTCs in T2 and Larger Breast Cancers A. Bhattacharyya, S. Krishnamurthy, A. Lodhi, C.S. Hall, I. Bedrosian, H.M. Kuerer, A.E. Anderson, S.A. Jackson, A. Lucci.* *Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Disseminated tumor cells (DTCs) in the bone marrow and circulating tumor cells (CTCs) have been identified in stage I-III breast cancer (BC) patients and predict survival. This study determined if these cells predict overall survival (OS) and relapse-free survival (RFS) in patients based on tumor size. Methods: Clinical stage I-III BC patients from a tertiary cancer center consented for blood (7.5 ml x 2 tubes) and bone marrow (10 ml from bilateral iliac crests) collection at the time of their primary BC surgery. DTCs were considered positive if one or more CK-positive cells in the bone marrow

assessed using an anti-cytokeratin antibody cocktail following Ficoll enrichment and cytospin, meeting morphological criteria for malignancy were found. CTCs were detected using the CellSearch™ system. Two or more cells per 7.5 ml blood were considered positive, since a threshold in non-metastatic BC has not yet been established. Results: We prospectively evaluated 446 patients. Mean age was 53 years, and median follow-up was 30 months. Forty-three percent of patients (192) had T1 tumors, 35% (155) T2, 10% (44) T3, and 12% (53) had T4 disease. Positive lymph nodes were identified in 47% (141/312) patients. In 30% (109/366) of patients DTCs were seen and 2 or more CTCs in 9% (34/393). In patients with tumor size > 2cm, 14% (8/56) of DTC positive patients died compared to 3% (5/153) of those who did not have DTCs (p=0.001). Similarly, 28% (5/18) of those who had 2 or more CTCs died compared to 6% (12/208) of those who did not (p=0.002). Although DTCs did not significantly predict RFS, 50% (9/18) of patients with 2 or more CTCs relapsed compared to 10% (20/208, p<0.0001) with CTCs < 2. DTCs and CTCs did not predict outcome when tumor size was < 2cm, as event rate was low in these patients (see table). There was no significant correlation between DTCs and/or CTCs with other primary tumor characteristics. Conclusions: In patients with tumor size > 2cm, both DTCs and 2 or more CTCs predicted OS. Two or more CTCs also predicted RFS in these patients. Multi-center studies with higher number of events are needed to determine if these tests are predictive in patients with T1 tumors.

Table 1: Overall and relapse-free survival classified by tumor-size and microscopic disease

Characteristic	Tumor > 2cm		P value	Tumor < 2cm		P value
	# DTC+	# DTC-		# DTC+	# DTC-	
Number enrolled	56	153	n/a	53	104	0.15*
Mean Age (years)	52	52	0.58^	53	54	0.65^
Death	8	5	0.001	1	1	0.73
Relapses	10	15	0.11	1	2	0.91
Characteristic	Tumor > 2cm		P value	Tumor < 2cm		P value
	# 2 or more CTC+	# 2 or more CTC-		# 2 or more CTC+	# 2 or more CTC-	
Number enrolled	18	208	n/a	16	151	0.57*
Mean Age	50	52	0.29^	55	55	0.97^
Death	5	12	0.002	0	3	0.43
Relapses	9	20	<0.0001	0	5	0.30

*chi-square test; ^t-test; other p values are logrank test for survival

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Risk Categorization of Women with Node Negative Early Stage Breast Cancer by Tumor Size M. Azu,[1]* P.A. George,[2] S. Chandwani,[2] K. Demissie.[2] *1. Surgery, Division of Surgical Oncology, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; 2. University of Medicine and Dentistry of New Jersey, School of Public Health, Department of Epidemiology, Piscataway, NJ.*

INTRODUCTION: In node negative breast cancer patients, tumor size is a powerful prognostic indicator. Risk groupings of breast cancer patients by tumor size are often done on the basis of survival findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP). However, it is unclear how the risk group specific cut-off values in NSABP were determined. Due to advances in treatment, the utility of the NSABP risk categories may not be applicable; and they may also vary by race, age, and hormone receptor status. These categorizations are important for counseling patients on their prognosis. METHODS: Non- Hispanic white and non-Hispanic black women ≥ 18 years of age with node negative early-stage breast cancer diagnosed between 1994 and 2007 were selected from the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registry. Spline regression was used to estimate tumor size cut-off values that predict a 5 year cumulative survival estimate. The cut-off values that reflected an important change in survival were chosen. The data was adjusted for tumor grade and stratified for risk groups based on race, age and hormone receptor status. RESULTS: The analyses included 151,427 patients (White: 138,729; Black: 12,698). The tumor size cut-off values vary by race, age and hormone receptor status (Table 1). The cut-off values predicting a 95% survival were 22mm for younger black hormone positive women; 7mm for older black hormone negative women; 41mm for younger white hormone positive women; and 7mm for older white hormone negative women. Among women with same tumor size, prognosis was poor for blacks as compared to whites, and for hormone negative women as compared to hormone positive women. CONCLUSIONS: Traditional stage based classification may not be an accurate means to assess risk in node negative breast cancer patients. Our findings support the adoption of tumor size cut-off values developed on the basis of age, race and hormone receptor status in counseling node negative breast cancer patients on their prognosis.

Table 1. Five year survival estimates for tumor size cut-off values by risk categories

Risk Category	Tumor Size Cut-off Values (mm)	5 year survival % (95% CI)
Black, Hormone Positive, ≥ 50 years of age	1	99.2 (98.3, 100.0)
	15	97.0 (96.1, 97.9)
	22	95.1 (93.9, 96.3)
	35	93.0 (91.0, 95.1)
	68	91.0 (86.0, 96.3)
	95	89.0 (78.9, 100.0)
Black, Hormone Negative, < 50 years of age	1	97.2 (94.0, 100.0)
	7	95.1 (92.0, 98.3)
	11	93.1 (90.4, 95.8)
	14	91.3 (88.8, 93.9)
	18	89.2 (86.2, 92.2)
	44	87.1 (83.0, 91.4)
	62	85.0 (79.7, 90.7)
	76	83.1 (74.3, 92.9)
	89	81.1 (67.9, 96.8)
White, Hormone Positive, ≥ 50 years of age	1	99.3 (99.1, 99.6)
	21	96.9 (96.7, 97.2)
	41	95.0 (94.5, 95.5)
	72	93.0 (91.5, 94.4)
	95	91.0 (88.2, 93.8)
White, Hormone Negative, < 50 years of age	1	95.8 (93.8, 97.9)
	7	95.0 (93.8, 96.2)
	17	92.9 (91.8, 94.0)
	23	90.7 (89.6, 91.8)
	28	89.0 (87.5, 90.5)
	38	86.9 (84.9, 89.0)

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Pain Pumps in Patients Undergoing Mastectomy Do Not Decrease Pain Scores or Narcotic Use E. Han,[1]* P. Matsen,[2] N. Johnson,[4] T. Wagie,[4] K.T. Morris.[3] *1. Surgery, OHSU, Portland, OR; 2. OHSU, Portland, OR; 3. University of New Mexico, Albuquerque, NM; 4. Legacy Cancer Services, Portland, OR.*

Introduction: Lidocaine pain pumps are used in many patients undergoing mastectomy in an attempt to reduce post-operative pain and narcotic requirements. However, there is limited non-industry sponsored literature assessing their efficacy. The aim of this study was to determine if the use of pain pumps for patients undergoing mastectomy led to decreased inpatient pain scores and narcotic use. Methods: IRB approval was obtained. Records of all women undergoing mastectomy during 2005-2008 at a tertiary care community based Cancer Center were evaluated for inclusion. Patients were stratified by unilateral vs bilateral operations and whether or not they had immediate reconstruction (RECON). Median pain scores (0-10) and narcotic use for patients receiving pain pumps were compared to those who did not have pain pumps by t-test. Narcotic use was confirmed by review of both pharmacy medication release and nursing administration records. Different narcotics were compared by converting them into their equivalent dose of morphine sulfate (MS). Results: 429 patients were identified; 423 charts were available for review. Patients with PCAs (n=13, 8 with pain pumps) were excluded due to unavailable dosage data, leaving 410 patients in the study. Median age was 54 (range 26-92). 298 received pain pumps (Pump) and 112 (No pump) did not. Mean age and stage were not significantly different between the two groups (p=1 and p=0.7, respectively.) The median inpatient pain score for post-operative days (POD) 0 and 1 was 2.5, indicating good pain management for the entire group. Median total MS equivalent dose over that time was 32.6 mg. Table I summarizes the differences between the two groups with p=NS. Entire Cohort n=410 Pump (n=298) No pump (n=112) Median POD 0-1 Pain Score (0-7.7) 2.5 2.5 2.5 Median MS equivalent POD 0-1 (0-582) 32.6 33.8 31 Median MS equivalent entire hospital stay / LOS (0-291) 15 14.9 15 Median LOS (1-10) 3 3 2 Conclusion: The use of pain pumps for patients undergoing mastectomy, whether unilateral or bilateral, with, or without immediate reconstruction, did not decrease pain scores or narcotic use.

	Entire Cohort (n=410)	Pump (n=298)	No pump (n=112)
Median POD 0-1 Pain Score (0-7.7)	2.5	2.5	2.5
Median MS equivalent POD 0-1 (0-582)	32.6	33.8	31
Median MS equivalent entire hospital stay / LOS (0-291)	15	14.9	15
Median LOS (1-10)	3	3	2

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Impact of Breast Cancer Stage on Outcomes following Mastectomy with Reconstruction A.K. Seth,[1]* E.M. Hirsch,[1] N.M. Hansen,[2] N.A. Fine.[1] *1. Northwestern University, Feinberg School of Medicine, Division of Plastic Surgery, Chicago, IL; 2. Northwestern University, Feinberg School of Medicine, Lynn Sage Comprehensive Breast Center, Chicago, IL.*

Introduction: Breast cancer staging, following mastectomy, is traditionally used to measure patient tumor burden and predict long-term survival. However, the relationship between tumor stage and short-term postoperative outcomes is unclear. This study evaluates complication rates following mastectomy and immediate reconstruction in patients stratified by breast cancer stage. Methods: Retrospective review of 897 consecutive patients from 4/1998-8/2008 at one institution yielded 682 (830 breasts) that underwent mastectomy and implant reconstruction with evidence of malignancy on pathology. Prior to analysis, patients were grouped by stage (group 1: stage 0 and I, group 2: stage II and III). Stage IV patients were excluded. Complications were calculated per breast and categorized by type and end-outcome, including non-operative (no further surgery) and operative (further surgery except explantation). For patients exposed to post-mastectomy radiation therapy (PMRT), complications were measured before and after treatment. Fisher's exact test, Student t-test, and multiple linear regression were used for statistical analysis. Results: Patients with higher stage tumors (group 2, n=340) had significantly more modified radical mastectomies and PMRT than lower stage tumor patients (group 1, n=342) ($p<0.0001$). Mean follow-up was 37.0 months. Regression analysis, adjusted for age, body mass index, smoking, and pre- or postoperative radiation, demonstrated that group 2 patients were at increased risk of total complications ($p=0.0005$), including infection ($p=0.004$), seroma ($p=0.02$), mastectomy flap necrosis ($p=0.02$), and explantation ($p=0.004$). Furthermore, tumor stage also affected the number of non-operative, operative, and total complications that occurred before PMRT exposure ($p=0.007$, $p=0.02$, $p=0.01$, respectively). Conclusions: Our review demonstrates that elevated breast cancer stage may correlate with increased complication rates following mastectomy and breast reconstruction. This relationship appears to be independent of radiation therapy exposure. Breast cancer staging should be discussed with patients as both an indicator of prognosis and a potential predictor of surgical risk.

Multiple linear regression, Stage II or III

Complication	OR	95% CI	p
Total Complications	1.84	1.30-2.60	0.0005
Hematoma	1.30	0.51-3.33	0.54
Infection	2.38	1.29-4.38	0.004
Seroma	2.30	1.11-4.78	0.02
Mastectomy Flap Necrosis	1.74	1.10-2.76	0.02
Non-operative	1.72	1.09-2.72	0.03
Operative	1.70	1.14-2.55	0.01
ECF	2.00	1.24-3.22	0.004
OR: odds ratio; CI: confidence interval; ECF: explantation or conversion to flap			

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Morbidity of Staged Proctectomy after Hepatectomy for Colorectal Cancer: A Matched Case-Control Analysis C.D. Tzeng,* G.J. Chang, S.A. Curley, J. Vauthey, L.M. Ellis, J.M. Skibber, B.W. Feig, E.K. Abdalla, T.A. Aloia, Y. You, M.A. Rodriguez-Bigas. *The U.T. MD Anderson Cancer Center, Houston, TX.*

Background: Proctectomy after hepatectomy, or the "reverse approach," is an alternative to traditional sequencing for advanced liver metastases with asymptomatic colorectal primaries. However, perioperative morbidity from staged proctectomy remains uncharacterized. We sought to identify risk factors for morbidity in these patients. Methods: A single-institution colorectal database was queried for patients treated with proctectomy after previous hepatectomy from 2003-2011. Reverse approach patients (31) were matched 1:2 with a cohort of standard proctectomy patients (62), using operation, age, sex, and surgeon. Perioperative factors were analyzed by univariate/multivariate models for associations with complications graded by Dindo-Clavien criteria. Results: 31 patients with adenocarcinoma ≤20 cm from the anal verge underwent proctectomy after hepatectomy. Median time from hepatectomy to proctectomy was 5.1 mo. Median tumor distance was 8.5 cm from the anal verge. No patients with primary tumors in situ recurred in the liver while awaiting proctectomy after hepatectomy. Prior to proctectomy, there were 28 (90%) major hepatectomies and 7 (22%) portal vein embolizations. Grade ≥2 complications developed in 42% of reverse approach and 27% of standard proctectomies ($p=0.17$). Grade 3 complications developed in 10% and 8%, respectively ($p=1.00$). There were no perioperative deaths. Reverse approach patients did not differ from the control cohort in operation, demographics, body mass index (BMI), comorbidities, tumor distance, operative time, estimated blood loss (EBL), length of stay, or complication rates ($p>0.05$). Independent predictors of Grade ≥2 complications were BMI ≥30 ($p=0.007$), operative time ≥300 min ($p=0.012$), intraoperative transfusion ($p=0.044$), concurrent procedures ($p=0.024$), and age ≥50 ($p=0.030$). Independent factors for Grade 3 complications were operative time ≥300 min ($p=0.015$), intraoperative transfusion ($p=0.011$), and EBL ≥300 ml ($p=0.047$). Conclusions: Risk factors for morbidity of staged proctectomy are similar to those for standard proctectomy. When applied to selected patients, the reverse approach is safe with acceptable morbidity.

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Ultra Low Anterior Resection following Neoadjuvant Chemoradiation for Rectal Cancer: The End of the 1-cm Rule? W.P. Ceelen,* P. Elshout, D. Vande Putte, Y. Van Nieuwenhove, N. Van Damme, P. Pattyn. *Ghent University Hospital, Ghent, Belgium.*

Introduction Controvery persists concerning the oncological safety of very close distal margins in patients with low (≤5 cm from the linea dentata)) rectal cancer treated with neoadjuvant chemoradiation (nCRT). Methods All patients with low rectal cancer treated with nCRT (45 Gy in 25 fractions with 5-FU) followed by sphincter saving surgery were identified from a prospective database. We analysed pathological and surgical outcome including local recurrence rate. Also, we studied the influence of distal margin (>1 cm versus ≤1 cm) on overall survival using log rank analysis. Data are expressed as mean±SD or median (range). Results From 1998 until 2010, 109 patients (73% male) were identified. Clinically, 59 % were staged as node positive. The pre-CRT distance from the anal verge was 3 cm (0.3-6). All patients underwent ultra low anterior resection; 35% underwent intersphincteric resection and coloanal anastomosis. A protective ileostomy was constructed in 90% of patients. Pathological stage distribution was as follows: stage 0 (ypCR): 16%, stage I, 30%, stage II, 21% and stage III, 19%. The median distal margin was 10 mm (0.1- 40mm). After a median follow up of 33 months, isolated local recurrence developed in 2 patients (1.8%) one of whom underwent successful surgical salvage. Two patients (1.8%) developed local and distant recurrence, while metastatic disease only developed in 25 patients (23%). Overall 5 year survival was 70%, and did not differ between a distal margin >1 cm versus ≤1 cm ($P=0.18$, log rank). Conclusions In patients with low rectal cancer undergoing nCRT, a distal margin <1 cm does not compromise local control or survival.

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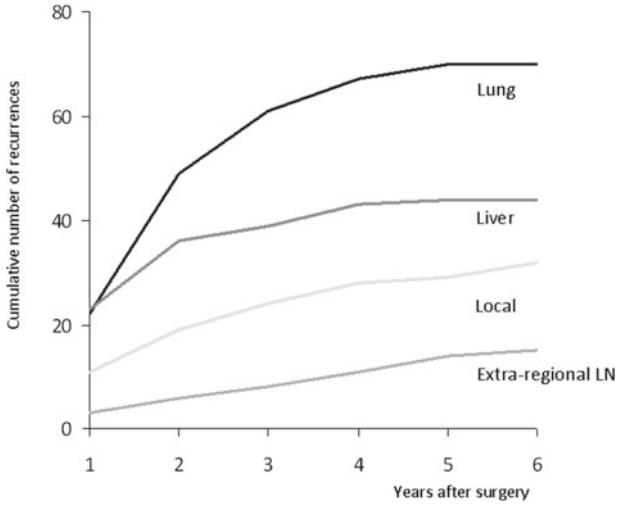
Recurrence Patterns after Multidisciplinary Therapy for Rectal Cancer in 725 Patients I. Park,* Y. You, J.M. Skibber, M.A. Rodriguez-Bigas, B. Feig, S. Nguyen, G.J. Chang. *University of Texas, MD Anderson Cancer Center, Houston, TX.*

Objective: Little is known about recurrence patterns after preoperative chemoradiotherapy (CXRT) for locally advanced rectal cancer. The aim of this study was to evaluate recurrence patterns of rectal cancer following CXRT and radical resection. Methods: A retrospective consecutive cohort study was performed of patients with clincal stage II-III rectal cancer treated with CXRT followed by radical resection between 1993 and 2008. All patients were followed with clinical examination including CEA every 3-6 months and radiographic evaluation of the chest, abdomen, and pelvis every 6-12 months. Results: 725 patients met criteria and were identified. Median tumor distance from the anal verge was 5 cm (interquartile range [IQR], 3-8). After median follow-up of 69 (IQR: 39-104)months, 155 patients (21.4%) recurred. A single site was involved in 132 (85.7%) and multiple sites in 23 (14.3%) patients. The most common site of initial recurrence was lung (n=70, 45.2 %) followed

by liver (n=44, 28.4%) and local (n=31, 20%). Time to recurrence (TTR) was median 17 (IQR: 9-30) months; 11 for liver, 17 for lung, 22 for local, and 48 for extraregional nodes (p=.02). By 2 years 101 (69%) and by 3 years 127 (82%) of all patients with recurrences had been identified. CEA was normal in 74% with recurrence including 72% of patients with initially elevated CEA. Salvage resection was performed for 68 (45.6%), of whom 38 (55.9%) experienced secondary recurrence. Median secondary TTR was 21 (IQR; 12-32) months, most commonly lung (n=31, 44.3%). A third (34.3%) of patients with re-recurrence had multi-site re-recurrence. Conclusions: For patients with stage II-III rectal cancer treated with CXRT and radical resection, the lung, and not liver, was the most common site of both primary and secondary recurrences. Most recurrences occurred within 3 years with the shortest median TTR for liver. Despite a high preop CEA, surveillance CEA did not reliably identify recurrence. These findings emphasize the importance of active surveillance including dedicated chest imaging.



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Predicting Postoperative Morbidity following Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CS + HIPEC) with preoperative FACT - C (Functional Assessment of Cancer Therapy) and Patient Rated Performance Status
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Background: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is associated with a substantial degree of perioperative morbidity and mortality. Our ongoing quality of life (QOL) trial seeks to describe the prognostic value of QOL measures for predicting postoperative morbidity and mortality following CS+HIPEC. Methods: - QOL and clinical data for all patients treated for peritoneal carcinomatosis and who participated in our QOL trials from 1991-2011 were analyzed. Patients completed the colon specific, plus the four subscales of the FACT questionnaire and the ECOG Performance Status Rating prior to CS + HIPEC. Trial outcome index (TOI) is a specific measure of function, symptoms and physical well-being of the patient, and is a combination of the physical, and functional well being subscales + the colon specific subscale of the FACT-C. Results: 387 (45.2%) of 855 patients participated in the QOL trials. Mean age was 53.3 yrs, 213(55%) were female vs. 174(45%) males. 240(62%) had a complication vs. 147(38%) who had no complication. A thirty day mortality rate of 5 % (43) was documented. Patients who suffered a 30-day postoperative mortality demonstrated a lower mean preoperative score in the FACT-C TOI 52.7 vs. 61.7 p<0.001. Independent predictors of 30-day mortality on multivariate analysis included TOI (0.05), age (0.001) and smoking (0.001). Patients with a higher TOI score were 0.9 times less likely to suffer a mortality (95% CI 0.9-1.0, p=0.05). The emotional well being (EWB) subscale showed a significant association with increased risk of postoperative complications, Patients with a higher EWB score were less likely to suffer a complication 0.9 (95% CI 0.87-1.0, p=0.04). Other Independent predictors of postoperative morbidity included diabetic status (p=0.05), ECOG performance status, (0.001), and gender (0.02). Conclusions: Preoperative QOL as measured by FACT-C and ECOG performance, added to traditional factors helps predict postoperative morbidity and mortality following CS +HIPEC.

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Assessment of Neoadjuvant Chemotherapy on Operative Parameters and Outcome in Patients with Peritoneal Dissemination from High Grade Appendiceal Cancer
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Introduction: High grade appendiceal adenocarcinoma (HG App Ca) is a rare malignancy with a propensity for early peritoneal dissemination (PD); morbidity and mortality is usually due to disease progression within the abdomen. The impact of neoadjuvant chemotherapy (neoadj chemo) on operative cytoreduction (CRS) and intraperitoneal chemotherapy (HIPEC) and patient survival was reviewed. Methods: Forty-five patients with PD from HG App Ca (M:27, F:18; mean age: 55 years [range: 40-85]) who were evaluated and treated from 2006-2011 were identified by retrospective chart review. All patients had a laparotomy with intent to undergo CRS and HIPEC; 26 received neoadj chemo (58%) and 29 (64%) received post-op chemo. Operative parameters, complications, and survival outcomes were analyzed. Results: Twenty-six patients received neoadj chemo consisting of a 5-FU based regimen with irinotecan or oxaliplatin $\pm$ bevacizumab; 15 (58%) had a clinical benefit defined by a >50% decrease in biomarkers, radiographic evidence of disease regression, or both; 9 (34%) had stable disease, and 2 (8%) had progression. The overall median peritoneal cancer index (PCI) in 45 pts was 27 (range: 2-35). Thirty (67%) had a complete or near complete cytoreduction (CCR score 0-1) and 37 (82%) received HIPEC with mitomycin-c. There was no difference in PCI, CCR score, operative blood loss, or major organ resection between those who received or did not receive neoadj chemo. Operative time was significantly shorter in those who did not receive neoadj chemo (p<0.02, mean OR time 325$\pm$163 minutes versus 438$\pm$134 minutes). Major complications and length of hospital stay were not different between the groups. The median actuarial overall survival was 39.6 months from time of diagnosis of PD (range: 3.2-173.2 months). Conclusion: Neoadj chemo has marked clinical activity in patients with PD from HG App Ca and is associated with longer operative times but does not adversely affect operative outcomes. Together these data support conducting a prospective clinical trial to define the role of neoadj chemo on patient survival in this clinical setting.

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Significance of Serum Tumor Marker Levels in Peritoneal Carcinomatosis of Appendiceal Origin
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Introduction: The significance of tumor markers in patients with peritoneal carcinomatosis (PC) of appendiceal origin is poorly defined. We sought to determine the prevalence and significance of pre- and post- operative tumor marker levels in patients undergoing cytoreductive surgery (CRS) and heated intraperitoneal chemoperfusion (HIPEC). Methods: We reviewed 282 patients undergoing CRS/HIPEC for appediceal PC from a prospective database. Pre- and post-CRS tumor marker levels were correlated with tumor characteristics and oncologic outcomes. Kaplan Meier survival curves and multivariate Cox-regression models were used to identify prognostic factors affecting oncologic outcomes. Results: Pre-operative serum levels were available as follows: CEA, 157 patients; CA19-9, 111 patients; CA-125, 106 patients. Preoperatively, at least one tumor marker was elevated in 70% of patients tested; CEA, 54.1%; CA19-9, 47.7% and CA-125, 47.2% of patients. Among patients with elevated pre-operative tumor marker levels, normalization occurred post-operatively in 79.4% for CEA, 92.3% for CA19-9 and 60% for CA-125. Absolute preoperative tumor marker levels correlated with peritoneal carcinomatosis index (p<0.0002). Elevated postoperative CEA level was predictive of disease recurrence (90% vs. 44%; p=0.001) and was associated with decreased progression-free survival (3-year PFS 42% vs. 7%; p=0.001). Most patients with preoperative elevation of one tumor marker also had elevation of another tumor

marker. Conversely, patients with normal preoperative levels of one tumor marker demonstrated a 24-45% chance of having elevation of another tumor marker. On multivariate Cox-regression analysis, elevated preoperative CA19-9 was associated with shorter overall survival [HR 3.7(1.3-10.6), p=0.02]. Conclusions: We recommend obtaining CEA, CA 19-9 and CA 125 on all appendiceal cancers. Most patients will have at least one elevated tumor marker preoperatively and will normalize post-CRS/HIPEC, allowing for ongoing surveillance. In addition, elevated postoperative CEA predicts disease recurrence and elevated preoperative CA 19-9 predicts poor overall survival.

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Restaging with Chest and Abdominal CT-scan after Neoadjuvant Chemo Radiotherapy for Locally Advanced Rectal Cancer: Is It Necessary? N. Ayez,[1]* J.W. Burger,[1] A.M. Eggermont,[3] J.J. Nuyttens,[4] R.S. Dwarkasing,[2] F.E. Willemssen,[2] C. Verhoef.[1] *1. Surgical oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 2. Erasmus MC, Division of radiology, Rotterdam, Netherlands; 3. Institut de cancérologie Gustav Roussy, Villejuif, France; 4. Erasmus MC Daniel den Hoed Cancer Center, Division of radiotherapy, Rotterdam, Netherlands.*

Background: There is no guideline regarding restaging of patients with locally advanced rectal cancer (LARC) after neoadjuvant long course (chemo)radiotherapy (CTxRTx) This study evaluates the value of restaging with Chest and abdominal CT-scan after CTxRTx. Patients and methods: Between January 2000 and December 2010, all newly diagnosed patients in our tertiary referral hospital who underwent a long course of (CTx)RTx for LARC were analyzed. Patients were included if they had a chest and abdominal imaging before and after neoadjuvant CTxRTx treatment. Results: A total of 153 patients who met the inclusion criteria and were treated with curative intend were included. A change in treatment strategy due to new findings on the CT scan after CTxRTx regarding metastases was observed in 18/153 patients (12%). Twelve patients (8% of 153 patients) were spared rectal surgery due unresectable metastatic disease. Conclusion: This study suggests that restaging with a chest and abdominal CT-scan after CTxRTx for LARC is advisable, since additional findings often alter treatment strategy.

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Interaction of Radiation with CpG Based Peptide Vaccination in a Spontaneous Murine Tumor Model K.W. Hamzeh,* H.J. Mauceri, T.E. Darga, R.R. Weichselbaum, M.C. Posner, Y. Meng. *University of Chicago, Chicago, IL.*

Background:Radiation therapy (RT) is an important treatment for breast cancer. Patients with large tumors or inflammatory carcinoma fail locally and with distant metastasis. Immune therapy combined with RT might improve local and distant control. Our purpose was to determine if combined therapy with RT and CpG based tumor vaccine could induce rejection of established rat-neu (RNEU) expressing Tubo mammary tumors in a spontaneous tolerant murine model. Method:Balb-neuT mice, a transgenic line expressing the activated form of RNEU as 'self-antigen' develop multiple spontaneous Tubo tumors. Mice were followed until the development of palpable tumors (7-8mm) at which point treatment was initiated with weekly peritumoral CpG and Rat-neu peptide, CpG alone, peptide alone or saline. The mice received 15Gy (tumor) 2 weeks into treatment. Results:The tumor growth of mice treated with RT plus CpG and peptide was effective. 60% of mice were completely cured, however no mice treated with RT alone or CpG and peptide alone were cured. Mice from this combined treatment group developed significantly fewer total number of new tumors compared to those from other treatment groups (p=0.0046), and showed a trend towards longer overall survival (p=0.084). Antibody depletion experiments in wild type balb/c tumor transplant system demonstrated that depletion of CD8+, CD4+ and NK cells abrogated this response. Tumor draining lymph nodes were harvested and co-cultured in vitro with saline, peptide or tumor. IFN-γ release was greater in the combined treatment group in response to both peptide and tumor. Conclusion:The addition of local RT to CpG based peptide vaccination induced cures of established Tubo tumors. The systemic nature of this enhanced immune response was suggested by the observation that the mice treated with this combination therapy also developed fewer total numbers of tumors at sites distant to the irradiated tumor. This immune effector response was shown to be peptide and tumor specific and dependent on CD8+, CD4+ and NK cells. These data provide proof of concept for the combined use of radiation and CpG based peptide vaccination as a powerful therapeutic strategy.

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Non-invasive Radiofrequency Field-induced Hyperthermia Sensitizes Murine Hepatocellular Carcinoma Xenografts after Targeted Delivery of Gemcitabine M. Raoof,* S.A. Curley. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: Gemcitabine is the single most effective nucleoside analogue against solid tumors. However, development of resistance is rapid. Alternative strategies are needed to minimize toxicity and enhance efficacy. In this study we utilize 10nm gold nanoparticles (AuNPs) as a scaffold to synthesize 2-in-1 nanoconjugates bearing a targeting antibody (cetuximab, C225) and gemcitabine. The release of gemcitabine is triggered by acidic pH. Non-invasive radiofrequency (RF) mediated deep-tissue hyperthermia is used to enhance the anti-tumor activity of gemcitabine delivered by targeted nanoparticles. METHODS: Two-in-one gold nanoconjugates were synthesized and analyzed using XPS. MTT assay was used to assess cytotoxicity in SNU449 and Hep3B cells lines. A Kanzius field RF generator was used for all RF experiments (600W, 13.56MHz). An ectopic Hep3B xenograft model was established in BalbC/Nu mice. RESULTS: Loading efficiency of gemcitabine on gold nanoconjugates was 20-30%. Of the total bound, 35% was released at pH 6 as opposed to 10% at pH 7.4 ($p<0.05$). Hep3B and SNU449 cells demonstrated selective cytotoxicity after targeted delivery as compared to isotype control particles-bearing gemcitabine and equimolar gemcitabine alone that was enhanced by non-invasive RF exposure. In mouse experiments, combination of targeted 2-in-1 gold nanoconjugates halted the growth of subcutaneous Hep3B xenografts in combination with hyperthermia (Figure 1). These xenografts demonstrated increased apoptosis and necrosis compared to controls. CONCLUSIONS: Targeted delivery of gemcitabine using 2-in-1 gold nanoconjugates demonstrated anti-tumor efficacy which was found to be superior to untargeted gold nanoparticles bearing gemcitabine with and without RF-mediated hyperthermia. Gemcitabine concentrations used in these experiments are ~250 times lower than that achieved with current clinically relevant dosages, indicating the importance of targeted drug delivery coupled with non-invasive RF hyperthermia to enhance tumor control while minimizing toxicity.

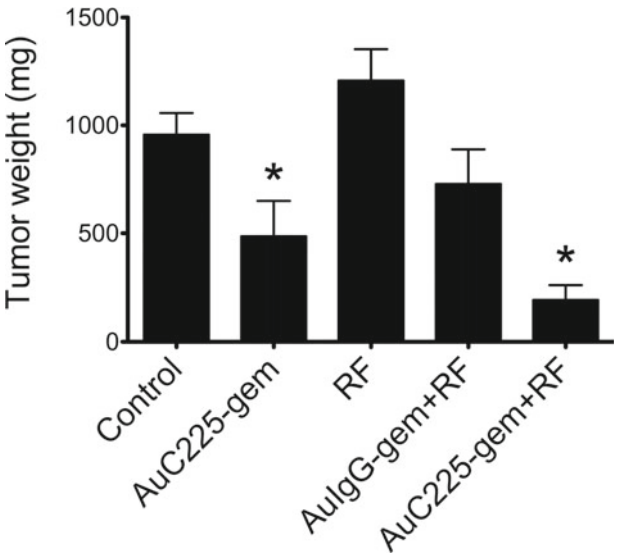

Figure 1. Efficacy of 2-in1 nanoconjugate (AuC225-gem) with and without radiofrequency field-induced hyperthermia against subcutaneous Hep3B xenografts implanted in mice (n=5-8). (*$p<0.05$ v RF alone)

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IL-13 Neutralizing Antibody Reduces Fibrosis and Improves Lymphatic Function in Chronic Lymphedema J.C. Zampell,* A. Yan, T. Avraham, E. Weitman, S. Aschen, B.J. Mehrara. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Chronic lymphedema is characterized by fibrosis and lymphatic dysfunction; however, mechanisms regulating the pathogenesis of this disease are unknown. We have shown that lymphedema is associated with T cell inflammation and a T-helper2 (Th2) biased response. Th2 responses are regulated in part by IL-13 and studies with humanized IL-13 antibodies show promise in treatment of fibrotic disorders. The purpose of this study was to determine the effect of IL-13 blockade in the progression of lymphedema in a mouse model. Methods: A mouse model of lymphatic fluid stasis was used in which superficial and deep lymphatics of the tail are disrupted leading to progressive lymphedema over 12 weeks. Animals were then treated with systemic IL-13 blocking antibody or isotype control for 6 weeks. Tail volume and dermal thickness measurements were used to determine lymphedema progression. Microlymphangiography and lymphoscintigraphy were used to evaluate lymphatic function. Scar index was determined from sirius red immunohistochemistry. Results: IL-13 blockade resulted in reduced tail volume as compared to isotype-treated controls at each post-operative time period (30.8% reduction by week 2, $p<0.01$; 41.9% reduction by week 6, $p<0.001$). These findings correlated with reduced dermal thickness (25.6% reduction, $p<0.05$) at post-operative week 6. Animals receiving IL-13 demonstrated a 25.5% reduction in scar index ($p<0.05$) 6 weeks post-operatively as compared to controls, demonstrating an overall reduction in fibrosis. Microlymphangiography revealed improvements in flow of fluorescent lymphatic tracer across the site of lymphatic disruption. Finally, lymphoscintigraphy revealed a 4.9-fold increase ($p<0.001$) in proximal lymph node uptake of lymphatic tracer following IL-13 blockade, indicating improved lymphatic flow. Conclusions: These results show that IL-13 blockade reduces fibrosis and improves lymphatic function thereby decreasing lymphedema progression. IL-13 blockade significantly decreased tissue edema and lymphatic fluid stasis, suggesting that targeted modulation of immune responses may represent a novel strategy of preventing or treating lymphedema.

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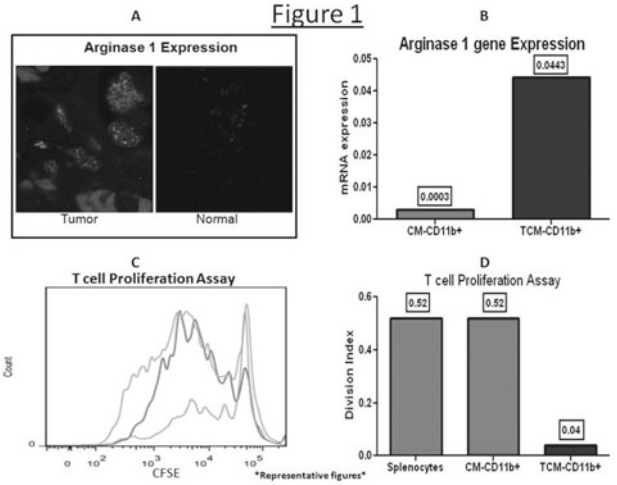
Tumor-derived Factors Induce Bone Marrow-derived Myeloid Cells to become Immunosuppressive in Pancreatic Cancer D.E. Sanford,* J. Mitchem, B. Belt, G. Lin, P. Goedegebuure, D. Linehan. *Hepatobiliary Surgery, Washington University in St. Louis, St. Louis, MO.*

Introduction: Pancreatic adenocarcinoma (PA) is a deadly malignancy known for its ability to recruit immunosuppressive myeloid cells (MCs) to the tumor microenvironment. One of the primary mechanisms that these MCs use to induce immunosuppression is the production of arginase 1 (Arg1) which degrades arginine, an amino acid critical for T cell activation and division. In this study, we show that tumor conditioned media from pancreatic cancer cells induces bone marrow (BM)-derived CD11b+ cells to upregulate Arg1 expression and suppress T cell proliferation. Methods: Immunofluorescence staining (IFC) was performed for Arg1 and CD14 expression in human PA and normal pancreatic tissue. BM-derived CD11b+ cells were isolated from the femurs of C57BL/6 mice using magnetic bead isolation. For 96 hours, CD11b+ cells were cultured in either complete media alone (CM-CD11b+) or complete media supplemented with tumor conditioned media from Pan02 murine pancreatic cancer cells (TCM-CD11b+). RT-PCR was then performed to quantify Arg1 gene expression. Next, a standard T cell proliferation assay was performed using carboxyfluorescein succinimidyl ester (CFSE)-labeled splenocytes from C57BL/6 mice stimulated with anti-CD3 antibody in the presence of TCM-CD11b+ or CM-CD11b+ cells. After 72 hours, flow cytometry was used to quantify CFSE expression and calculate the division index (average number of divisions that responding cells underwent). Results: IFC of human PA revealed the presence of infiltrating MCs that abundantly expressed Arg1 compared to normal pancreatic tissue (Fig. 1A). In mice, TCM-CD11b+ cells significantly upregulated Arg1 gene expression compared to CM-CD 11b+ cells [0.0443 vs 0.0003; $p<0.05$] (Fig. 1B). TCM-CD11b+ cells inhibited T cell proliferation when co-cultured with stimulated splenocytes as demonstrated by CFSE dilution and a markedly reduced division index compared to splenocytes co-cultured with CM-CD11b+ cells [0.04 vs 0.52] (Fig. 1C&D). Conclusion: Pancreatic cancer cells secrete soluble factors that induce BM-derived CD11b+ MCs to become immunosuppressive, and these cells are likely significant contributors to tumor immune evasion.



A) Normal human pancreas and pancreatic adenocarcinoma tissue were stained for Arginase 1 and CD14 by immunofluorescence. (Green= Arginase 1+, Red=CD14+) B) Bone marrow-derived CD11b+ cells from C57BL/6 mice were cultured in complete media alone (CM-CD11b+) or in complete media supplemented with Pan02 conditioned media (TCM-CD11b+). After 72 hours, the level of Arginase 1 gene expression was measured by RT-PCR. p-value<0.05 C) Splenocytes from C57BL/6 mice were labeled with CFSE, co-cultured with CM-CD11b+ or TCM-CD11b+ cells, and stimulated with anti-CD3 antibody. After 72 hours, flow cytometry was performed to evaluate T cell CFSE expression. (Red=Splenocytes alone, Blue=splenocytes with TCM-CD11b+ cells, Yellow=Splenocytes with CM-CD11b+ cells) D) The T cell division index, the average number of divisions that responding T cells underwent, was calculated based on the degree of CFSE dilution.

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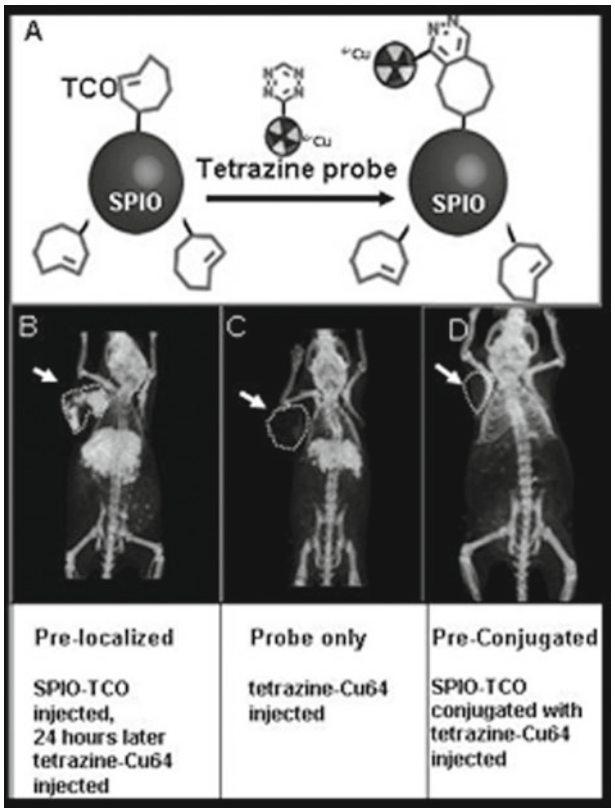
MicroPET Evaluation of In Vivo Biorthogonal Click Chemistry Reaction between a Radiolabeled Tetrazine Probe and TCO-modified Nanoparticles M. Girgis,[1] W.Y. Lin,[3] S. Hou,[3] M. Rochefort,[2] C. Shen,[3] J.S. Tomlinson.[1]* *1. UCLA, Division of Surgical Oncology, Los Angeles, CA; 2. VA Greater Los Angeles, Department of Surgery, Los Angeles, CA; 3. UCLA, Molecular and Medical Pharmacology, Crump Molecular Imaging Institute, Los Angeles, CA.*

Introduction: Nanoparticles are able to concentrate within solid tumors via the enhanced permeability and retention (EPR) phenomenon associated with cancer tissue and can be functionalized with a wide variety of agents. In this study we use MicroPET to evaluate the ability of a novel radiolabeled small molecule probe to covalently react in vivo with the chemically modified surface of nanoparticles which have already localized to the tumor via EPR. Methods: Supraparamagnetic iron oxide nanoparticles (SPIO) were chemically modified to display transcyclooctyne (TCO) on its surface. A tetrazine derivative (N-(4-(1,2,4,5-tetrazin-3-yl)benzyl)-4-benzamide) was developed and conjugated to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) for copper-64 [64Cu] radiolabeling. The TCO-modified-SPIO was reacted with [64Cu]-tetrazine in vitro and monitored by radioHPLC to confirm fast reaction kinetics. The [64Cu]-tetrazine probe was evaluated for its ability to locate and covalently bind to TCO-modified-SPIO nanoparticles in vivo by utilizing a mouse subcutaneous xenograft model(U87). Control groups included preconjugated nanoparticles and [64Cu]-tetrazine probe only. MicroPET/CT was performed 24 hours after tail vein injection of the probe. Radioactivity was

measured in blood and tumor to provide objective confirmation of the microPET images. Results: The percent coupling of [64Cu]-tetrazine with TCO-modified SPIO was 95% at 15min. Percent of injected dose/gram of tissue (%ID/g) in U87 tumors and blood was 1.56 and 0.42 in mice with pre-localized SPIO, 0.67 and 0.28 with probe only, and 0.67 and 0.28 when preconjugated SPIO was injected. Conclusion: We demonstrate evidence to support the occurrence of an in vivo biorthogonal click chemistry reaction between a radiolabeled tetrazine probe and a TCO modified nanoparticles utilizing PET. Comparing %ID/g between pre-localized nanoparticles with probe only, we show 2.5X more radioactivity in the tumor. This strategy can be utilized to perform in vivo delivery of functional agents to the surface of nanoparticles that have accumulated in tumors through EPR.



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2G8, a TGFβR2 Inhibitor, Blocks TGF-β Signaling and Migration in an Immunocompetent Pancreatic Cancer Model K.T. Ostapoff,* B. Cenik, R.E. Schwarz, R.A. Brekken. *Surgical Oncology, University of Texas Southwestern, Dallas, TX.*

TGF-β functions as a tumor suppressor early in the development of pancreatic ductal adenocarcinoma (PDAC) but during tumor progression after undefined molecular changes TGF-β switches to a promoter of metastasis, tumor angiogenesis and epithelial to mesenchymal transition (EMT.) A potential strategy is to target TGFβR2, one of the major signaling receptors for TGF-β. 2G8 is a anti-rat monoclonal antibody that binds specifically to and blocks murine TGFβR2. Protein expression was analyzed using Western Blot. Cell proliferation was analyzed using Cell Titer Blue Assay and migration was determined using transwell migration assay. EMT protein expression was determined by ICC. PanO2-HY cells were used to establish an orthotopic and splenic metastasis model. In an orthotopic model, mice received Saline, Gemcitabine (Gem), 2G8 or 2G8 + Gem. For splenic metastasis model,mice received 2G8 on post injection day -1, +1 or +7 days or control IgG. At baseline, PanO2-HY cells express TGFβR2, alk5 and alk1 and express high levels of zeb1 and β-catenin. 2G8 inhibits phosphorylation of smad2, ERK1/2 and p38 but not smad1/5 in vitro. 2G8 did not inhibit cell proliferation but did inhibit cell migration in vitro. After 7 days of treatment with 2G8, PanO2-HY cells had reduction in nuclear zeb1 staining by ICC. In the orthotopic model, 2G8 significantly inhibited metastasis to liver, peritoneum and gastrointestinal tract(p=0.02). In splenic metastasis assay, 2G8 treated mice livers weighed significantly less than control treated mice (p=0.0005). In the group of mice treated prior to tumor cell injection, none of them developed a primary tumor. Conclusion: Inhibition of TGFβR2 with 2G8, results in inhibition of smad2 dependent pathways as well as non-canonical TGF-β signaling in vitro. By inhibiting tumor cell migration in vitro and reducing EMT transcription factors, 2G8 may result in delayed tumor progression. In vivo data in both orthotopic and metastatic models suggest that inhibition of TGF-β signaling via TGFβR2 inhibits tumor cell metastasis. Further analysis are being conducted to understand changes within primary tumor and metastasis within this model.

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Pre-clinical Testing of anti-KIT Designer T-cells for the Treatment of Gastrointestinal Stromal Tumor S. Naheed, A. Bais, N. Ahmed, C. Nguyen, L. Licata, N. Espat, R. Junghans, S. Katz.* *Roger Williams Medical Center, Providence, RI.*

Introduction: Imatinib mesylate is an effective treatment for metastatic gastrointestinal stromal tumor (GIST), but development of resistance is a significant problem. Immunotherapy using designer T cells (dTc) has recently gained increased attention for several malignancies. Preclinical testing for anti-KIT dTc to target GIST cells is being performed in our laboratory. **Methods**: Anti-KIT dTc were engineered by retroviral transduction with a novel chimeric antigen receptor (CAR). The gene for stem cell factor (SCF), the ligand for KIT, was cloned into our 1st generation (gen) (SCF-CD3ζ) and 2nd gen (SCF-CD28-CD3ζ) CAR constructs. In vitro dTc proliferation and KIT+ tumor (GIST882 and 48) lysis were measured by flow cytometry, and IFNγ by ELISA. Human GIST tumors were implanted into immunodeficient mice that were infused with anti-KIT dTc. **Results**: The 1st and 2nd gen anti-KIT CAR were successfully manufactured and transduced into murine and human T cells (see table for statistics). When co-cultured with KIT+ tumor, 44% of 1st gen and 71% of 2nd gen dTc from mice proliferated. Murine dTc were able to effectively lyse two human KIT+ GIST cells lines. 1st and 2nd gen human dTc also proliferated in the presence of GIST882 and 48, at levels significantly higher than when cultured with KIT- control cells (39% and 47%). Both the 1st and 2nd gen human dTc produced IFNγ in the presence of KIT+ GIST. Human dTc were efficient at lysing GIST 882 and 48 in vitro compared to untransduced T cells. To test the in vivo activity of human anit-KIT dTc, we treated mice with established subcutaneous GIST882 tumors. Treatment via tail vein with either 1st or 2nd gen human anti-KIT dTc led to a significant decrease in tumor growth compared to mice treated with untransduced T cells. **Conclusion**: A functional and novel anti-KIT CAR has been constructed to produce dTc that demonstrate specific activity against KIT+ GIST in vitro and in vivo. Further studies, inclusive of a phase 1 clinical trial are warranted to further demonstrate the full therapeutic potential and safety of anti-KIT dTc.

Murine dTc	1st gen	2nd gen	CTRL
% Transduced	26.9 ± 7.6	27.3 ± 7.1	N/A
% Divided	44.1 ± 5.0, p<0.001	71.2 ± 9.8, p<0.001	22.9 ± 0.1
% Residual tumor fluorescence (MFI^)	612.7 ± 48.7, p=0.009	514.0 ± 14.4, p<0.001	901.0 ± 36.3
Human dTc	1st gen	2nd gen	CTRL
% Transduced	33.3 ± 3.5	30.4 ± 3.5	N/A
% Divided	39.4 ± 1.6, p<0.001	46.8 ± 3.8, p<0.001	12.6 ± 0.7
IFNγ(pg/ml)	462.0 ± 21.9, p=0.002	475.2 ± 6.4,p<0.001	0.6 ± 0.2
% Residual tumor fluorescence (MFI^)	156.0 ± 16.3, p<0.001	44.0 ± 8.5, p<0.001	1055 ± 114.9
Subcutaneous tumor size at 40 days (mm^2)*	65.2 ± 9.2 (n=6, p=0.03)	69.6 ± 17.4 (n=10, p=0.04)	99.1 ± 10.3 (n=10)

^Tumor cells were labeled with a green cytoplasmic dye (CFSE) and loss of mean fluorescence intensity (MFI) was used to measure cell lysis. *Linear regression analysis confirmed that the overall growth curves for 1st gen and 2nd gen dTc were significantly different from control T cells.

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A Novel Xenograft Model of Gastrointestinal Stromal Tumor (GIST) J.K. Sicklick,* S.Y. Leonard, E. Mose, R.P. French, M. Criscuoli, D.V. Jaquish, K. Maruyama, R. Schwab, D.A. Cheresh, A.M. Lowy. *University of California, San Diego, La Jolla, CA.*

INTRODUCTION: GIST treatment with imatinib has served as the prototype for targeted molecular therapy. However, patients frequently acquire drug resistance to imatinib and this has prompted the development of additional multi-kinase inhibitors. To date, preclinical testing of novel agents has predominantly been performed using cell line based subcutaneous xenografts that may overestimate drug activity in the clinic. This suggests that novel in vivo models are needed to improve prediction of clinical efficacy. We hypothesized that human GISTs could be intra-peritoneally xenografted into immunodeficient mice in order to better recapitulate the microenvironment and biology of GIST. METHODS: Tumor acquisition was performed under an IRB-approved protocol. Following tumor resection, we anesthetized NOD-scid (NS) or NS gamma (NSG) mice and performed a midline laparotomy. 2×2 mm tumor fragments were sutured into the abdominal viscera of NS (N=10) or NSG (N=15) mice. Tumors were imaged every 3-4 wks with ultrasound (US). 2 mice were also evaluated with PET scan. RESULTS: We have xenografted GISTs from 3 patients into 25 mice with an 80% success rate and 4% perioperative mortality. We observed tumor progression in the liver (9/10), renal capsule (8/10), lesser sac (2/3), or gastric wall (1/2) of mice. This included 14 primary xenografts and 11 passaged xenografts. At 21-196 d (median 46 d), tumor size averaged 473±736 mm3 (median 104 mm3, range 2.2-2683 mm3) by US. In addition, 30% (6/20) of mice developed metastatic disease based upon US, necropsy, histology and/or KIT immunostaining. We also determined that 2/2 tumors were FDG-avid on PET. CONCLUSIONS: To our knowledge, we report the first intra-peritoneal xenograft model of human GIST using patient-derived tumor tissue. This novel in vivo approach is a reproducible model of human GIST that replicates the tumor microenvironment, heterogeneity, and metastatic potential of a human GI sarcoma. As compared to current research tools/models, this approach may allow researchers to better predict chemotherapeutic responses, further understand the tumor biology of GIST, and serve as a means to propagate additional tumor tissue for subsequent experimental analyses.

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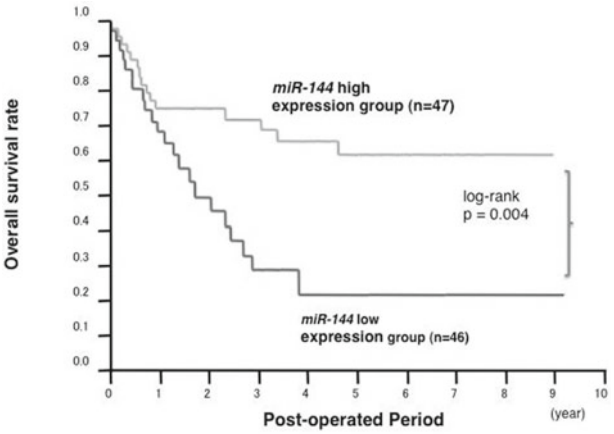
Clinical Significance of mir-144-ZFX Axis in Isolated Tumor Cells in Bone Marrow in Gastric Cancer Cases K. Mimori,[1]* G. Sawada,[1] T. Fukagawa,[2] M. Fabbri,[3] M. Iwatsuki,[1] T. Yokobori,[1] N. Nishida,[1] H. Iinuma,[4] M. Sasako,[2] C.M. Croce,[3] M. Mori.[5] *1. Surgery, Kyushu University Beppu Hospital, Beppu, Oita, Japan; 2. National Cancer Center Hospital, Tokyo, Japan; 3. Ohio State University, Columbus, OH; 4. Teikyo University, Tokyo, Japan; 5. Osaka University, Suita, Japan.*

Purpose: We previously reported that bone marrow (BM) was a homing site for gastric cancer (GC) cells leading to hematogenous metastases. There has been little study that microRNAs regulated pathways in malignant cells or host cells in BM, and thereby regulated the progression of GC. Experimental Design: Both microRNA microarray and gene expression microarray analyses of total RNA from BM were conducted, comparing five early and five advanced GC patients. We focused on miR-144-ZFX axis as a candidate bone marrow regulator of GC progression, and validated the origin of the microRNA expression in diverse cell fractions (EpCAM+CD45-, EpCAM-CD45+, and CD14+) by magnetic activated cell sorting (MACS). Results: Quantitative RT-PCR analysis validated diminished miR-144 expression in stage IV GC patients with respect to stage I patients (t-test, $p = 0.02$), with an inverse correlation to ZFX (ANOVA $p < 0.01$). Luciferase reporter assays in five GC cell lines indicated their direct binding. Pre-miR-144 treatment and the resultant repression of ZFX in GC cell lines up-regulated their susceptibility to 5-FU chemotherapy. In MACS-purified BM fractions, the level of miR-144 expression was significantly diminished in isolated tumor cell fraction ($p=0.0005$). Diminished miR-144 expression in 93 cases of primary GC indicated poor prognosis. Conclusions: We speculate that disseminated cancer cells could survive in BM when low expression of miR-144 permits up-regulation of ZFX. Thus, the regulation of the miR-144-ZFX axis in cancer cells plays a key role in the metastatic cascade in GC.



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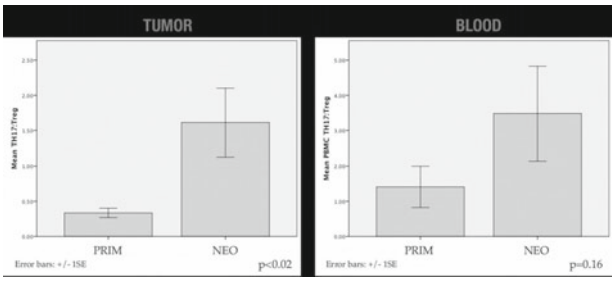
Neoadjuvant Therapy of Pancreatic Cancer Promotes an Anti-tumor Immune Response V.G. Pillarisetty,[1]* K.C. Shibuya,[2] Y. Li,[2] A. Leahy,[3] S.H. Whiting,[4] C. Yee.[2] *1. Surgery, University of Washington, Seattle, WA; 2. Fred Hutchinson Cancer Research Center, Seattle, WA; 3. Seattle Cancer Care Alliance, Seattle, WA; 4. University of Washington, Seattle, WA.*

INTRODUCTION: Despite a dense immune infiltrate, pancreatic cancer (PC) stands out among gastrointestinal malignancies for its aggressive behavior and poor prognosis. Our aim in this study was to determine the mechanism of the failed immune response to PC and ability of neoadjuvant therapy to activate anti-tumor immunity. **METHODS:** Patients with PC who consented to our IRB-approved study and underwent primary resection (PRIM) or resection after neoadjuvant chemotherapy (gemcitabine-based) +/- chemoradiotherapy (NEO) were studied. Fresh tumor was minced and digested to create a single-cell suspension for flow cytometry. Peripheral blood collected at the time of resection was also studied. Data shown as mean ± std. error. Independent-samples T test used to determine significance. **RESULTS:** We collected adequate tumor tissue for flow cytometry from 13 patients (7 PRIM and 6 NEO). Tumors had a robust CD45+ immune infiltrate characterized by a high proportion of CD3+ T cells and a full complement of adaptive and innate immune cells such as dendritic cells and natural killer (NK) cells. CD25+FoxP3+ regulatory T cells (Treg), which have been implicated in the failure of anti-tumor immunity, were prevalent among CD4+ T cells in tumor (PRIM 19.4 ± 4.7%, NEO 8.2 ± 2.9%, p=0.08) and blood (PRIM 4.7 ± 2.3%, NEO 0.9 ± 0.5%, p=0.17). We confirmed that these putative Treg have the ability to suppress T cell and NK cell function in vitro. We also found that inflammatory IL-17-producing CD4+ T helper cells (Th17), believed to play a critical role in anti-tumor immunity, were present in tumor (PRIM 6.8 ± 3.2%, NEO 10.3 ± 4.4%, p=0.52) and blood (PRIM 6.8 ± 5.5%, NEO 1.6 ± 0.5%, p=0.40). As the balance of Th17 cells and Treg is important in immunoregulation, we analyzed the Th17:Treg ratio. Interestingly, there was a significant increase in the intratumoral Th17:Treg ratio with neoadjuvant therapy and a similar trend in the blood (Figure). **CONCLUSIONS:** Pancreatic cancer induces a tolerogenic immune response characterized by a low intratumoral Th17:Treg ratio. Neoadjuvant therapy significantly alters this relationship, thereby tipping the regulatory balance from immunosuppression to inflammation.



Neoadjuvant chemotherapy of pancreatic cancer tips the immunoregulatory balance from immunosuppression to activation. PRIM - primary resection, NEO - resection after neoadjuvant therapy.

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Epigenetic Regulation in Colon Cancer Stem Cells K. Ohta,[1]* N. Haraguchi,[2] H. Ishii,[2] M. Sekimoto,[1] Y. Doki,[1] M. Mori.[1] *1. Department of Gastroenterological surgery,Osaka university, Suita city, Osaka, Japan; 2. Department of Frontier Science for Cancer and Chemotherapy, Osaka university, Suita city, Osaka, Japan.*

Introduction; Cancer stem cells (CSCs) retains self-renewal ability and produce cancer cells, hence it has been believed to exist in cancer foci from cancer onsets. In contrast to classical CSCs concept, novel dynamic CSCs concept reported in melanoma study revealed that epigenetic regulation gives stemness properties to cancer cells. In this study, we aimed to confirm if epigenetic factors gives stemness properties to colon cancer cells, and if regulation of such factors induce disruption of cancer cell hierarchy. Methods; In the CD44+ALDH+ colon CSCs fraction and non-CSCs fraction, the expression of histone demethylase JARID1B and epithelial-mesenchymal transition (EMT) activator ZEB1 was confirmed in colon cancer cell lines. In the non-CSCs fraction, JARID1B and ZEB1 was transfected. Additionally, JARID1B and ZEB1 were silenced with shRNA in the CSCs fraction. Biological assessments includes tumorigenic assay were performed. Results; In the colon cancer cell line, JARID1B and ZEB1 were highly expressed in Colo201 and WiDr. RT-PCR and Western blot analysis revealed that the expression of JARID1B and ZEB1 was high in the CD44+ALDH+ colon CSCs fraction compared to that in non-CSCs fraction. By the treatment of shRNA of JARID1B and ZEB1, cell cycle was activated but decreased tumorigenic activity in severe immuno-deficient mice. In addition, chemo-radio sensitivity was increased by the treatment of shRNA. When JARID1B and ZEB1 was transfected to non-CSCs fraction, cell shape changed to spindle and tumorigenic activity was increased compared to control. Invasion assay also revealed that JARID1B and ZEB1 transfected non-CSCs increased invasiveness. Conclusion; In colon cancer, expression of JARID1B and ZEB1 change cellular character of non-CSCs to that of CSCs, suggested that epigenetic regulations have important roles to maintain CSCs. Further studies are necessary to identify what factors regulate JARID1B and ZEB1 in vitro.

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Microsatellite High Colorectal Cancer: Does the Underlying Mechanism for Instability Matter? J.R. Hyngstrom,* M.A. Rodriguez-Bigas, MD, G.J. Chang, MD, MS, M.W. Taggart, MD, J.M. Skibber, MD, B.W. Feig, MD, Y. You, MD. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Purpose: Microsatellite instability (MSI) testing in colorectal cancer (CRC) provides prognosis, predicts chemotherapy response, and guides diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. MSI can be sporadic or hereditary, arising from somatic or germline mutations in DNA mismatch repair (MMR) genes respectively. The clinical implications of these distinct mechanisms remain uncertain. Methods: Patients who underwent surgical resection of CRC and MSI testing between 2000 and 2011 were identified. MSI-high CRCs were defined by: pathogenic mutation in MMR genes; >30% of markers showing allelic shift in PCR-based tumor testing; or loss of expression in at least 1 MMR protein on tumor immunohistochemistry. The subset with MLH1 gene promoter methylation, BRAF mutation, or EPCAM mutation was considered sporadic. Clinicopathologic features and disease-free survival (DFS) were examined along with a cohort of microsatellite stable (MSS) CRCs. Results: MSI-high CRC's, including 92 germline and 49 sporadic, were compared with 105 MSS CRCs. Both germline and sporadic MSI-high CRCs more commonly arose proximal to the splenic flexure when compared to MSS CRCs (63% and 92%, vs. 30%; p<0.001). Both also more commonly exhibited pathologic features of mucinous/signet ring histology (40% and 47%, vs.16%; p<0.001) and lymphocytic infiltrate/Crohn's like reaction (15% and 49%, vs.7.6%; p<0.001). Further comparison between germline vs. sporadic MSI-high CRCs revealed significant differences by patient age, tumor location, and disease stage (Table). Moreover, sporadic MSI-high CRCs more often had poor prognostic features, i.e. poor differentiation and lymphovascular invasion (Table). No difference was observed in stage-stratified DFS between germline vs. sporadic MSI-high CRCs. Conclusion: Patients with sporadic MSI-high CRCs exhibit distinct clinicopathologic features compared to those with germline MSI-high tumors. Despite the presence of features associated with poor prognosis, no apparent survival difference was observed. Further characterization of these distinct groups is warranted to explain the discordance between risk factors and outcomes.

Comparison of Germline and Sporadic MSI-tumors

	Germline		Sporadic		
Clinical Characteristic	n	%	n	%	p-value
n	92		49		
Age Colon Resection (median)	43.7		65.9		<0.001
Gender, male	53	57.6%	20	40.8%	0.057
Tumor Location					
Proximal	58	63.0%	45	91.8%	<0.001
Descending/sigmoid/rectal	34	37.0%	4	8.2%	
Stage					
I	31	33.7%	6	12.2%	0.025
II	21	22.8%	18	36.7%	
III	21	22.8%	19	38.8%	
IV	9	9.8%	6	12.2%	
Grade					
Well/moderately	64	69.6%	23	46.9%	0.025
Poorly/undifferentiated	26	28.3%	25	51.0%	
Unknown	1	1.1%	1	2.0%	
Lymphovascular Invasion					
yes	31	33.7%	28	57.1%	0.007
no	61	66.3%	21	42.9%	
Lymphoid/Crohn's like reaction					
yes	14	15.2%	24	49.0%	<0.001
no	78	84.8%	25	51.0%	

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KRAS Codon 13 Mutations Predict Response to Neoadjuvant Chemoradiation Therapy in Patients with Rectal Adenocarcinoma M.N. Duldulao,* W. Lee, R. Nelson, W. Li, Z. Chen, J. Kim, J. Garcia-Aguilar. *General Oncologic Surgery, City of Hope, Duarte, CA.*

Background: The predictive role of KRAS mutation in therapeutic management of metastatic colorectal cancer has been much investigated. However, the association between KRAS mutations and rectal cancer response to neoadjuvant chemoradiation therapy (CRT) remains unclear. Our objectives were to determine the incidence of KRAS mutations in patients with rectal cancer and identify potential correlations with response to CRT. Methods:

Patients with Stage II-III rectal cancer (n=148) from a multicenter prospective clinical trial were assessed. DNA was extracted from pretreatment tumor biopsies; and genotyping of KRAS was completed by PCR and direct sequencing. All patients underwent pre-operative CRT followed by surgery; and treatment response was evaluated by a pathologist. Surgical specimens without evidence of residual disease were deemed to have a pathologic complete response (pCR). Results: Overall, 60 of 148 (40.5%) patients had KRAS mutation. Breakdown of the different KRAS mutations revealed that 40 (66.7%) mutations occurred in codon 12, 12 (20.0%) in codon 13, 5 (8.3%) in codon 61, and 3 (5.0%) in other locations. When examining the relationship between KRAS and CRT response, we observed that detection of any KRAS mutation was associated with a decreased rate of pCR compared to wild-type KRAS (13.3% vs. 33.0%, respectively; p=0.007) (Table 1). More specifically, patients with KRAS codon 13 mutations did not respond to CRT compared to non-codon 13 mutations (p=0.037). In contrast, the detection of codon 12 or codon 61 mutations was not associated with response to CRT(Table 1). Conclusions: Patients with KRAS mutation have lower response rates to CRT compared to patients with wild-type KRAS. However, our results indicate that this association does not apply to all KRAS mutations, rather to KRAS codon 13 mutation alone. Thus, these data are the first to show that patients with KRAS codon 13 mutations may not derive pCR from neoadjuvant CRT.

Table 1: KRAS Mutations and Response

KRAS Status	n	pCR n (%)	Non-pCR n (%)	p-value
Total	148	37 (25.0%)	111 (75.0%)	
KRAS wt	88	29 (33.0%)	59 (67.0%)	
KRAS mut	60	8 (13.3%)	52 (86.7%)	0.007
Codon 12	40	7 (17.5%)	33 (82.5%)	0.199
Codon 13	12	0 (0.0%)	12 (100%)	0.037
Codon 61	5	1 (20.0%)	4 (80.0%)	0.793

pCR - pathologic complete response; wt - wild-type; mut - mutant.

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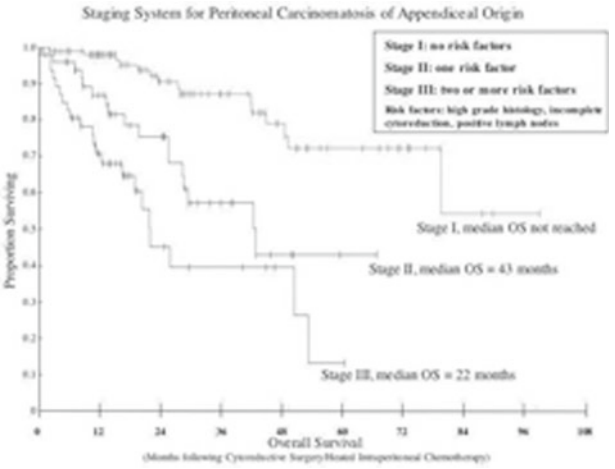
Development of a Prognostic Staging System for Peritoneal Carcinomatosis of Appendiceal Origin P.L. Wagner,* F. Austin, A. Mavanur, L. Ramalingam, H.L. Jones, M.P. Holtzman, S.A. Ahrendt, A.H. Zureikat, J.F. Pingpank, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Patients with peritoneal carcinomatosis (PC) of appendiceal origin demonstrate variable oncologic outcomes, despite aggressive cytoreductive surgery (CRS) and heated intraperitoneal chemoperfusion (HIPEC). We sought to devise a prognostic staging system for patient survival stratification after resection. Methods: We reviewed 197 patients undergoing CRS/HIPEC for treatment of appendiceal PC from a prospective database. Kaplan Meier survival curves and multivariate Cox-regression models were used to identify prognostic factors affecting oncologic outcomes. Clinicopathologic variables affecting overall survival were utilized to develop a prognostic staging system. Results: Univariate and multivariate Cox-regression analysis indicated that high grade tumor histology (HR=4.79, p=0.009), lymph node involvement (HR=2.87, p=0.009) and incomplete cytoreduction (HR for CC-2=5.31, p=0.001; HR for CC-3=3.19, p=0.005) were high-risk features, adversely affecting overall survival. Patients were divided into three groups, based on the presence or absence of one or more high-risk features: Stage I patients had no high-risk features (n=102); Stage II patients had only one high-risk feature (n=49); and Stage III patients had more than one high-risk feature (n=46). Median overall survival for Stage I was not reached, for stage II was 43 months and for stage III was 22 months. Five-year overall survival was 72%, 43% and 13% for stage I, II and III, respectively (p<0.0003 for Stage I vs. II and p=0.06 for Stage II vs. Stage III). (Fig 1) Conclusions: We propose a three-tier staging system for appendiceal PC following CRS/HIPEC, based on histologic grade, lymph node involvement and completeness of cytoreduction. Presence of any one or more of these high-risk features significantly decreased survival in our single-institution database and provided the basis for a prognostic staging system.



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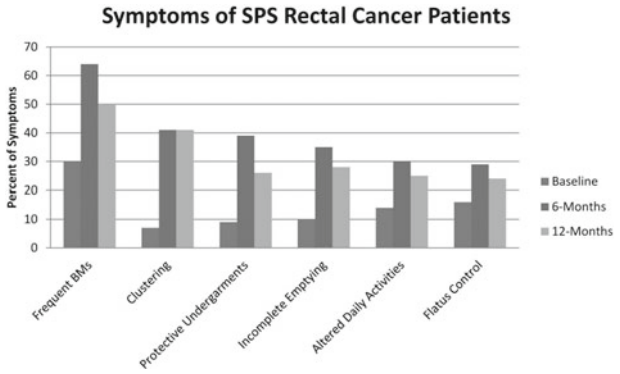
Understanding Bowel Dysfunction after Sphincter-preserving Surgery: Results from a Prospective Study H. Yeo,[1]* S. Patil,[1] P. Paty,[1] J. Guillem,[1] M. Weiser,[1] G. Nash,[1] D. Schrag,[2] L. Temple.[1] *1. Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; 2. Dana Farber Cancer Institute, Boston, MA.*

Background:Bowel function (BF) is altered after sphincter preserving surgery (SPS) for rectal cancer but has been poorly studied. Understanding postop BF could facilitate preop decision making and allow physicians to better manage long term function. Methods:A prospective longitudinal study of stage I-III rectal cancer patients undergoing SPS from 1/07-7/09. Patients completed the validated Bowel Function Instrument(BFI) and the EORTC-QOL at 6 month intervals after restoration of bowel continuity. Responses were scored and comparisons made at preop, 6 and 12-mos using MANOVA. Predictors of BFI 12-months post surgery were identified using the Mann-Whitney or Kruskal-Wallis test. Results:139 patients were eligible for enrollment. Response rates were good (preop 97%, 6-mos 79%, 12-mos 86%). Most patients were male(55%), had stage III(56%) rectal cancer, and received preop neoadjuvant therapy(78%). Baseline surveys were completed a median of 4.2 days prior to surgery. Coloanal was the most common anastomotic type(64%). Anastamoses were primarily stapled(71%), diverted(75%), without a pouch(67%), a median of 7.8 cm from the anal verge, and reversed at a median of 6 mos. The most common post-op symptoms were frequency(64%), clustering(41%) and the need to wear protective underwear(39%)(Table1). Compared across time, patients reported significantly worse BF with all BFI subscales(FREQUENCY p=0.05, URGENCY p<0.001, DIETARY p<0.004 and TOTAL BFI score p<0.001) being lower post-op with no significant change between 6 and 12 mos. Predictors of poor function at 12 mos included radiation, low tumors and hand sewn anastomoses(p-values=0.005, 0.009, and 0.006) while age, gender, and straight vs. pouch procedures were not associated with poor function. Global quality of life was high throughout with no significant change in the EORTC QOL subscale(p<0.15). Conclusions:Bowel dysfunction is common after SPS and, while QOL remains high, BF does not return to baseline. Limited improvement is seen between 6 mos. and 12 mos. Although additional follow-up is needed to further characterize long term outcomes, these data may be used to help council patients undergoing SPS.



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Patterns of Recurrence following Complete Response to Regional Chemotherapy for In-transit Melanoma K. Sharma,* G. Beasley, R. Turley, D. Tyler. *Duke University, Durham, NC.*

Background: Even after complete response (CR) to regional chemotherapy for in-transit melanoma, many patients develop recurrence. Understanding the probability, location, and timing of recurrences can optimize management strategies for this patient population. Methods: A prospective database identified 214 patients who underwent 81 first-time hyperthermic isolated limb perfusions (HILPs) and 133 first-time isolated limb infusions (ILIs) for in-transit melanoma. Response was defined using the Response Evaluation Criteria in Solid Tumors; recurrence was defined as development of new disease after exhibiting an in-field CR. All tests were two-sided with a level of significance of $\alpha = 0.05$. Results: HILP was more likely to produce an in-field CR than ILI (44% vs. 28%, p = 0.01). By 3-year follow-up, 65% of 36 HILP-CRs [95% CI: 43-79%] and 85% of 37 ILI-CRs [95% CI: 63-94%] developed recurrence. Median time to first recurrence was longer for HILP-CR than ILI-CR (23 months vs. 8 months, p = 0.02). There was no statistically-significant difference in median time to first in-field recurrence between HILP-CR and ILI-CR (46 months vs. 25 months, p = 0.15), but HILP-CR showed a longer median time to first out-of-field recurrence over ILI-CR (42 months vs. 14 months, p = 0.02). Finally, HILP-CR exhibited a clinically-significant OS benefit over ILI-CR (3-yr. survival: 77% vs. 54%, p = 0.10, See Figure). Conclusion: In the largest series comparing patterns of recurrence after regional chemotherapy, we demonstrate that the prognosis for patients achieving a CR from HILP is different than the prognosis for patients who achieve a CR after ILI. Complete responders after HILP appear to have an OS benefit and delayed out-of-field recurrence compared to complete responders after ILI. However, control of in-field disease after CR is similar with both treatment modalities.

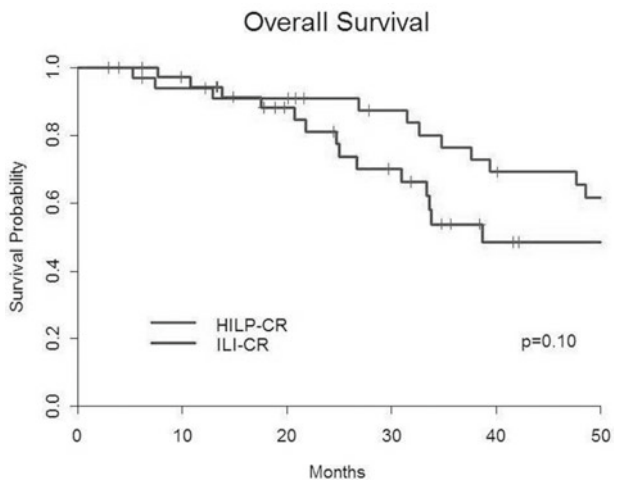

Figure 1. Kaplan-Meier plot comparing overall survival (OS) following complete response to HILP vs. ILI

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In-transit Melanoma Metastases: Incidence, Prognostic Importance and Implications for Patient Staging R. Read, L.E. Haydu, B. Le Mesurier, R.P. Saw, J.F. Thompson.* *Melanoma Institute Australia, North Sydney, NSW, Australia.*

Introduction The prognostic significance of in-transit metastases (ITM) in patients with melanoma is not well documented in the literature, and accurately staging patients with ITM has therefore been difficult. In this study we sought to document the incidence of ITM in a large, single institution experience and analyze the factors influencing the prognosis of patients who developed ITM. Methods Of the 15218 patients who received definitive treatment for a single primary cutaneous melanoma at the Institute between January 1994 and December 2009, 505 patients who subsequently developed ITM were identified. Data pertaining to the primary melanoma, sentinel node (SN) status, pattern of disease progression and patient outcome were analysed. Results The median primary tumor Breslow thickness for the patients who developed ITM was 2.95mm and 39.4% were ulcerated. The overall rate of ITM was 3.3%. The rate was 0.3% for patients with primary melanomas <1mm, 6.6% for patients with primaries ≥ 1mm and 5.9% in patients undergoing SN biopsy. A positive SN was associated with an ITM rate of 17%. The median time from primary diagnosis to the development of ITM was 17.9 months. After ITM diagnosis the median survival time was 19.9 months, with a 5 year survival (5YS) of 32.8% and a 10YS of 27.5%. After ITM diagnosis only primary site and ulceration of the primary melanoma were predictors of survival. 5YS rates after ITM diagnosis according to primary site and ulceration are shown in the Table. Conclusions One in 15 patients with melanomas ≥1mm thick developed ITM in this large study. The diagnosis of ITM had serious prognostic implications, with a median survival of only 19.9 months. 5YS from ITM diagnosis was determined primarily by primary tumor site and ulceration, ranging from 47.9% when the primary was non-ulcerated and on a limb to only 13.6% for an ulcerated primary on the trunk. The data from this and similar studies should assist the Melanoma Staging Committee of the AJCC to assign melanoma patients with ITM appropriately in the next edition of the AJCC Staging Manual.

Site of Primary Melanoma	Limb (n = 247)	Head/Neck (n = 90)	Trunk (n = 119)
Non-ulcerated Primary	47.9%	30.8%	28.6%
Ulcerated Primary	24.1%	25.4%	13.6%

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Scalp Melanoma: Responsible for the Poor Prognosis of Head and Neck Melanoma? J. Ozao-Choy,* J.M. Hiles, J.L. Yoon, M.S. Sim, M.B. Faries, D.L. Morton. *John Wayne Cancer Institute, Santa Monica, CA.*

INTRODUCTION: Previous studies have shown that head and neck melanomas have worse disease-free and overall survival compared to non-head and neck melanomas. However, the relative impact of scalp versus non-scalp location is unclear. We hypothesized that the scalp is associated with an outcome profile that not only distinguishes it from any other anatomic site but also is responsible for the generally poor prognosis of head and neck melanoma. METHODS: Our cancer center's melanoma database was queried for all primary cutaneous melanoma patients presenting for treatment between 1971 to 2010. The Kaplan-Meier method was used to assess the role of location on distant disease-free interval, disease-free and overall survival. Chi-square test evaluated the role of location on local recurrence. Multivariate COX proportional hazards models were used to control for the effect of age, male sex, Breslow thickness, lymph node status, and ulceration when evaluating the role of location on melanoma-specific survival. RESULTS: 799 primary scalp melanomas were treated between 1971 and 2010 and survival data were obtained (Table1). Scalp melanomas had significantly more local recurrence ($p<0.0001$) and distant metastases ($p<0.0001$) compared to face and neck (n=1249), trunk (n=6236) and extremity (n=3112) melanomas. Scalp melanomas also had significantly worse disease-free survival ($p<0.0001$) and overall survival ($p<0.0001$). On multivariate analysis, scalp location was an independent predictor of melanoma specific survival (HR 1.52, CI 1.22-1.91, $p<0.0003$). CONCLUSIONS: We report the largest series of scalp melanoma to date.

Scalp melanomas have a poor disease-free and overall survival compared to melanomas of the face and neck, trunk and extremities. Scalp melanomas may warrant further studies to ascertain whether biology or anatomy contributes to their worse clinical course. In addition, scalp melanomas need closer clinical follow-up.

5 year disease-free and melanoma-specific survival rates

Primary Site	n	5 year DFS	5 year MSS	Multivariate analysis MSS, p-value	Multivariate analysis HR, CI
Scalp	799	46.9%, CI(43.2-50.5)	64.5%, CI (60.9-67.9)	0.0003*	1.52, CI(1.22-1.91)
Face/Neck/Ear	1249	62.7%, CI(59.8-65.5)	78.3%, CI (75.8-80.7)	0.50	0.91, CI(0.70-1.19)
Trunk	6236	66.5%, CI (65.2-67.6)	77.5% CI (76.4-78.6)	0.46	1.06, CI(0.91-1.23)
Extremity	3112	68.6%, CI (66.9-70.3)	82.0% CI (80.5-83.3)	**	**

DFS- disease free survival, MSS- melanoma specific survival, CI-95% confidence interval, HR-Hazard Ratio
*p value <0.05 were considered statistically significant
**Reference group

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1 vs 2 cm Surgical Excision for 1-2 mm Melanomas: Does it Matter? L. Hudson,* G.W. Carlson, A. Hestley, D. Murray, M. Rizzo, S.K. Maithel, K.A. Delman. *Emory University, Atlanta, GA.*

Introduction: NCCN guidelines recommend one or two cm margins for melanomas 1 – 2 mm in depth based on comparative data from two different trials. No prospective head-to-head comparison has been performed. We hypothesized that 1 cm margins would not increase local recurrence or decrease recurrence-free survival (RFS) compared to 2 cm margins in patients with T2 melanomas. Methods: An institutional melanoma database was queried and a retrospective chart review performed to identify patients with 1 – 1.99 mm melanomas treated at our institution from 7/95 to 3/10. All patients were treated with wide excision and sentinel lymph node biopsy. Patients with undocumented surgical margins were excluded. Clinical, pathologic, and recurrence data were reviewed. Univariate and multivariate analyses were performed. Results: Of 2118 pts in the database, 755 pts met study criteria; 470 additional pts. were identified from chart reviews. 515 had complete data: 166 pts (32%) had 1 cm margins and 349 (68%) had 2 cm margins. Median follow-up time was 30.4 months. Median age was 51 yrs. 42% were female. Median tumor thickness was 1.28 mm in the 1 cm group and 1.46 mm in the 2 cm group (p = 0.46). Ulceration was the same in the 1 vs 2 cm groups (15.2% vs 20.3%, respectively; p = 0.22). There was no difference in the presence of a positive histologic resection margin: 3% in the 1 cm group and 0.6% in the 2 cm group (p = 0.72). There was no difference in local recurrence rates: 2.4% in pts with 1 cm and 0.9% in pts with 2 cm (p = 0.31). Regional recurrence was 3.6% vs 3.2% in the 1 vs 2 cm group respectively (p = 0.99). Multivariate analysis for both local recurrence and RFS was performed taking into account adverse tumor factors. Margin size was not associated with either local recurrence or decreased RFS; only ulceration was predictive of outcome (Table). Conclusions: In this series of patients with T2 melanomas 1 cm margin did not increase local recurrence or decrease RFS compared to 2 cm margins. As has been advocated by prior comparison between trials, a 1 cm margin for patients with T2 melanomas appears appropriate but a prospective, randomized trial analyzing this question would be optimal.

Local Recurrence	Hazard Ratio	95% CI	P Value
Margin	0.320	0.051 - 2.013	0.225
Ulceration	8.156	1.254 - 53.036	0.028
Mitoses (0 v ≥1)	2.263E7	0.00	0.996
Regression	0.350	0.036 - 3.442	0.368
Recurrence-Free Survival	Hazard Ratio	95% CI	P Value
Margin	0.559	0.272 - 1.146	0.112
Ulceration	3.149	1.502 - 6.6	0.002
Mitoses (0 v ≥1)	1.281	0.588 - 2.789	0.533
Regression	0.817	0.383 - 1.743	0.602

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Surgeons Opinions on Lymphadenectomy in Melanoma Patients with Positive Sentinel Node (SN): A Worldwide Web-based Survey S. Pasquali,[1]* J.F. Thompson,[1] J.H. De Wilt,[4] K. McCaffery,[3] M.J. Quinn,[1] C.R. Rossi,[2] R.P. Saw,[1] K.F. Shannon,[1] J.R. Stretch,[1] A.J. Spillane.[1] *1. Melanoma Institute Australia, Sydney, NSW, Australia; 2. Veneto Institute of Oncology, Padova, Italy; 3. Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia; 4. Radboud University, Nijmegen, Netherlands.*

Introduction: Although guidelines recommend completion lymph node dissection (CLND) or observation within a clinical trial for melanoma patients with positive SN, it has been reported that half of patients with positive SN undergo CLND in the USA. This multinational web-based survey of melanoma surgeons investigated patterns of management in SN positive patients. Methods: The survey was designed following input from a multinational group of surgeons. Cognitive interviews were used to refine the questions. Surgeons were identified by conducting a systematic-review of the literature on CLND in SN positive patients, and identifying the corresponding authors, who were invited to provide email addresses of all suitable surgeons belonging to their departments. Results: Of 337 surgeons invited, 192 (58%) from 25 countries responded. Most of them worked in a Surgical Oncology Unit (44%) or a University Hospital (50%). In patients with positive SN, 168 (92%) surgeons recommend CLND. The strength of the recommendation to undergo CLND is mostly influenced by patient's medical conditions (65%, n=118) and the extent of the SN involvement (60%, n=109). Seventy one responders (40%) randomize patients for the Multicenter Selective Lymphadenectomy Trial (MSLT)-II. The majority of them (76%, n=54) refer almost all patients in their practice for consideration of the trial. In the case of neck CLND, a full-level 1-5 dissection is suggested by 58 (35%) responders, while 103 (63%) base the extent of CLND on the primary site and lymphatic mapping. Three-level axillary CLND is performed by 80% (n=133) of responders. Inguinal only and ilioinguinal CLND are performed by 60 (36%) and 50 (30%) of surgeons, respectively. The remaining 58 responders (34%) select patients for combined inguinal and pelvic dissection according to the number of positive inguinal nodes, Cloquet's status and lymphatic drainage pattern. Conclusions: The majority of melanoma surgeons (92%) recommended CLND in SN positive patients. MSLT-II investigators report referring most patients for consideration of randomization. More evidence is needed to standardize neck and groin CLND recommendations.

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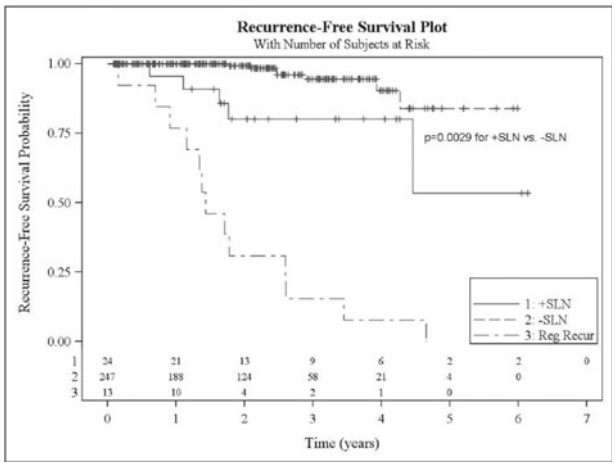
Sentinel Node Biopsy is Indicated for Thin Melanomas ≥0.76mm D. Han,[1]* S.S. Marzban,[1] D. Yu,[2] X. Zhao,[2] J.L. Messina,[1] R.J. Gonzalez,[1] C.W. Cruse,[1] A. Sarnaik,[1] C. Puleo,[1] V.K. Sondak,[1] J.S. Zager.[1] *1. Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL; 2. Department of Biostatistics, Moffitt Cancer Center, Tampa, FL.*

Introduction: A consensus for which patients (pts) with thin melanomas should undergo sentinel lymph node (SLN) biopsy (SLNB) has not been well established. We describe a large single institution experience with SLNB in pts with thin melanomas. Methods: Since 2005, SLNB has been routinely performed at this institution for melanomas ≥0.76mm. Retrospective review from 2005 to 2010 identified 284 pts with thin melanomas; SLNB was performed in 271 pts while 13 pts never had a SLNB but were referred for regional recurrence (RR) as first site of recurrence. Clinicopathologic characteristics were correlated with nodal status and outcome. Results: Median age was 55 years and 53% of pts were male. A +SLN was seen in 22/271 (8.1%) cases. Median Breslow thickness was the same at 0.85mm in pts with or without nodal metastases (+SLN and RR vs. -SLN). Of melanomas with a mitotic rate (MR) <1, a +SLN was seen in 7.8% of these cases. However, multiple regression analysis showed MR ≥1 correlated with a positive node (+SLN and RR vs. -SLN, p<0.05) and ulceration trended towards significance (p=0.055). Completion lymph node dissections (CLND) were performed in 15/22 +SLN pts and in all cases no additional positive nodes were found. Of the 7 pts who did not undergo CLND, 6 pts were enrolled in MSLT-2 and randomized to observation while 1 patient was lost to follow-up. Median follow-up was 2.2 years. Overall survival (OS)

was significantly worse for pts with a RR versus a -SLN ($p<0.001$) while OS was similar between pts with a +SLN versus a -SLN ($p=0.57$). However, recurrence-free survival was significantly ($p<0.005$) worse for pts with a +SLN versus a -SLN (Figure). Conclusions: Thin melanomas ≥0.76mm with a MR ≥1 have a higher risk for nodal metastases but the lack of this characteristic does not reliably exclude the chance for nodal metastases to <5%. Therefore, we feel SLNB is warranted for melanomas ≥0.76mm regardless of MR since detection of a +SLN identifies pts for potential systemic therapy and allows for treatment of nodal basins at an occult stage. In contrast, pts with thin melanomas and untreated occult nodal metastases that are allowed to progress to a RR appear to have significantly worse OS.



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Merkel Cell Carcinoma: A Genetic Analysis of Disease Prognosis

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Introduction: Due to the rarity of Merkel Cell Carcinoma (MCC), prospective clinical trials have not been practical. This study seeks to identify biomarkers with prognostic or clinical significance. Methods: Our tumor registry identified 62 patients who were treated for MCC at our institution. 18 patients had adequate formalin-fixed paraffin embedded (FFPE) archival tissue and adequate follow up. Patients were stratified into good, moderate or poor prognosis. A single dermatopathologist review these H&E slides. Using ArcturusXT Laser Capture Microdissection (Molecular Devices), tumor cells were isolated from the specific areas of interest. The captured tumor tissue was subjected to RNA extraction using the Invitrogen PureLink™ FFPE RNA Isolation Kit. The extracted RNA was analyzed for integrity with the Agilent Bioanalyzer then amplified and hybridized to Affymetrix GeneChip Human Exon 1.0 ST arrays using proprietary procedures from the NuGEN WT- Ovation™ FFPE System. Results: A total of 191 genes showed significant differential expression between the different prognostic groups. Several genes were identified that showed a significant difference in regulation between the good and poor prognosis groups (Table 1). Our study showed two major genes which have no previous association with MCC as well as some novel genes. Keratin 20 (KRT20) and Neurofilament protein (NEFM) have been identified in previous studies as proteins of interest in MCC. Our study showed these genes to be significantly upregulated in patients with a poor prognosis. Of interest, phospholipase A2, group X was upregulated in poor responders. Phospholipases liberate arachidonic acid from cellular membranes which can be metabolized to eicosanoids through three major pathways: the cyclooxygenase (COX), the lipoxygenase (LOX) and the cytochrome P450 monooxygenase pathways. This pathway has been implicated in several cancers. Conclusion: Recent studies of MCC have focused on identification of possible prognostic biomarkers. Our study identified genes which had not been previously identified in similar experiments. Future studies include confirmation of mRNA expression with polymerase chain reaction and immunohistochemical studies.

Table 1

Gene Symbol	Gene Name	Fold-Change (Poor vs. Good)
NEFM	neurofilament, medium polypeptide	4.32
PLA2G10	phospholipase A2, group X	3.55
KRT20	keratin 20	3.05
MBNL2	muscleblind-like 2 (Drosophila)	2.51
TCEA3	transcription elongation factor A (SII), 3	2.35
HMGB2	high-mobility group box 2	2.25
ZRSR2	zinc finger (CCCH type), RNA-binding motif and serine	2.23
RIMS2	regulating synaptic membrane exocytosis 2	2.15
MAL2	mal, T-cell differentiation protein 2	2.15
CISD2	CDGSH iron sulfur domain 2	2.11
MGC16384	hypothetical LOC114130	2.11
HIST1H4D	histone cluster 1, H4d	2.04
DDAH1	dimethylarginine dimethylaminohydrolase 1	2.03
EDN3	endothelin 3	-2.03
DCUN1D1	DCN1, defective in cullin neddylation 1, domain containi	-2.04
OMP	olfactory marker protein	-2.10
FGF9	fibroblast growth factor 9 (glia-activating factor)	-2.14
KRTAP21-1	keratin associated protein 21-1	-2.16
KIAA1217	KIAA1217	-2.39
KRTAP19-5	keratin associated protein 19-5	-2.89
MCART1	mitochondrial carrier triple repeat 1	-3.21
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	-3.32

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Merkel Cell Carcinoma: 30-Year Experience from a Single Institution

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PURPOSE: Merkel cell carcinoma (MCC) is a rare cutaneous malignancy with an aggressive natural history. Few single-institution series have been reported. METHODS: We reviewed the MCC patients treated at our institution between 1980 and 2010. Patient, tumor and treatment variables were analyzed to determine MCC-specific outcomes. RESULTS: We found 161 patients with adequate data. There was a 2.5-fold incidence increase over the last decade. The median length of follow-up was 22 months. The stage at diagnosis was 34% (I), 21% (II), 11% (IIIa), 23% (IIIb) and 10% (IV). The 5-year MCC-specific survival rates were 95%, 69%, 45% and 0% for stages I, II, III and IV, respectively. Distant metastasis developed in 4% patients with T1 (< 2 cm), 35% with T2 (2 – 5 cm) and 43% with T3 (> 5 cm) lesions. One-third of patients presented with pathological (IIIa, micrometastasis) or clinical (IIIb, macrometastasis) nodal disease. Sentinel lymph node biopsy (SLNB) found micrometastases in 10 out of 27 (37%) early-stage patients: 28% for stage I (4, n = 14) and 46% for stage II (6, n = 13). Recurrence developed in 50% of SLNB-positive (5, n = 10) and 29% of SLNB-negative (5, n = 17) patients. MCC-related mortality was 28% and 48% for stage IIIa and IIIb patients, respectively. Excluding stage IV patients, half of patients recurred with a median length to recurrence of 9 months. The proportions of first recurrence event were distant (50%), nodal (30%) and local (20%). Adjuvant radiotherapy and/or chemotherapy did not improve recurrence or survival rates. Notably, adjuvant radiotherapy did not reduce locoregional recurrence rates. One-third of patients died of the disease; this proportion remained unchanged over the study period. CONCLUSIONS: MCC incidence appears to be rising and prognosis remains poor. SLNB identifies micrometastasis in approximately one-third of early-stage patients. A negative SLNB may predict for an improved yet not necessarily favorable outcome. Initial tumor size and clinical nodal disease predict for poor outcome. Despite current aggressive locoregional therapies, adjuvant therapy may not decrease distant recurrence. Better markers of recurrence and treatment response for MCC are needed.

TABLE 1. Description of patient and tumor characteristics from 161 patients treated for Merkel cell carcinoma at MGH between 1980 and 2010

Variable	No. of Patients	%
Age (years)		
Median	72	
Range	28-97	
Sex		
Male	98	61
Female	63	39
Immunosuppression (n = 160)		
Yes	90	56
No	70	44
Location of primary tumor		
Head and neck	65	40
Lower extremity	36	23
Upper extremity	24	15
Trunk	12	7
Unknown	24	15
Size of primary (cm) (n = 136)		
Median	2.3	
Range	0.4-11.3	
Clinical stage at diagnosis (n = 160)		
I	55	34
II	34	21
IIIa	18	11
IIIb	37	23
IV	16	10
Recurrence (n = 144)		
No	77	53
Yes	67	47
Recurrence-free survival (months) (n = 67)		
Median	9	
Range	1.3-75.0	
Type of recurrence (n = 67)		
Local	14	21
Nodal	19	28
Distant	34	51
Follow up (months)		
Mean	44	
Median	22	
Range	0.1-300	
Stage at last follow-up		
NED	63	39
AWD	12	7
DOD	55	34
DOC	31	19
MCC related mortality		
Overall (n = 161)	55	34
1980 - 1990 (n = 19)	7	34
1990 - 2000 (n = 41)	11	27
2000 - 2010 (n = 102)	37	36

Abbreviations: NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; DOC, died of other causes.

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Survival after Resection of Malignant Eccrine Carcinoma: Risk Factors and Trends in Outcomes for 1045 Patients J.B. Avraham,[2]* D. Villines,[3] V.K. Maker,[4] C.Z. August,[5] A.V. Maker.[1] *1. University of Illinois at Chicago, Dept of Surgery, Division of Surgical Oncology; Creticos Cancer Center, Advocate Illinois Masonic Medical Center, Chicago, IL; 2. Advocate Illinois Masonic Medical Center, Creticos Cancer Center, Dept of Surgery, Chicago, IL; 3. Advocate Illinois Masonic Medical Center, Creticos Cancer Center, Dept of Research and Statistics, Chicago, IL; 4. University of Illinois at Chicago, Dept of Surgery; Advocate Illinois Masonic Medical Center, Dept of Surgery, Chicago, IL; 5. Advocate Illinois Masonic Medical Center, Creticos Cancer Center, Dept of Pathology, Chicago, IL.*

<p>**Introduction:** The current AJCC staging system does not individually address eccrine carcinoma. Due to its rarity, disease prognosis and optimal management strategies have not been well established. We performed a population-based study to determine the risk factors, survival, and optimal management of this skin malignancy. <p>**Methods:** Using Surveillance, Epidemiology and End Results population-based cancer registry data, we identified patients diagnosed with skin cancer between 1973 and 2008. Associations between risk factors, treatment modalities and survival were calculated using logistical regression, Kaplan-Meier estimates and log-rank analysis. <p>**Results:** Of 1045 patients identified with eccrine carcinoma, the incidence of distinct subtypes were: microcystic adnexal carcinoma (MAC) (32%), general eccrine adenocarcinoma (23%), hidradenocarcinoma (22%), porocarcinoma (19%) and spiradenocarcinoma (4%). Overall 5-year survival (OS) was 78%, while age-adjusted survival was 94%. Patients diagnosed with MAC had improved OS (87.3%) compared to patients with hidradenocarcinoma (61.9%, p=<0.001), spiradenocarcinoma (72.1%, p=0.01), porocarcinoma (78.3%, p=<0.001), and eccrine adenocarcinoma (80.1%, p=ns). The majority of patients were treated with surgical excision (85%) or surgery plus radiation (7%) with similar OS (78.0% vs. 75.7%, p=ns). The presence of positive nodes was associated with decreased survival (p=0.02), though nodal staging was rare. Patients with well or moderately-differentiated tumors demonstrated improved OS compared to those with high-grade disease (p=0.005). Patient race, tumor size, and tumor site were not associated with OS. <p>**Conclusions:** This large population-based appraisal identified that accurate histologic subtyping and pathologic grade were associated with 5-year survival in eccrine carcinoma, and should be specified in biopsies and excised specimens. Surgical excision is appropriate, and the addition of adjuvant radiation was not associated with improved survival. Though limited, our results may augment the AJCC staging system in determining prognosis for patients diagnosed with this skin cancer.

Clinicopathological Variables Associated with 5-Year Survival in Malignant Eccrine Carcinoma (n=1045)

<p align="left">Clinicopathological Variable	Hazard Ratio	95% CI	p-value
<p align="left">Race	0.803	0.164 - 3.945	0.44
<p align="left">Tumor Size	1.395	0.329 - 5.910	0.096
<p align="left">Tumor Location	1.811	0.596 - 5.504	0.83
<p align="left">Histological Subtype	1.094	0.861 - 1.391	<0.001*
<p align="left">Histological Grade	1.669	0.078 - 35.598	0.005*
<p align="left">Lymph Node Positivity	0.095	0.002 - 58.33	0.02*
<p align="left">Surgical Excision vs. Surgery+XRT	0.476	0.063 - 3.567	0.21

*= p<0.05, XRT = Radiation Therapy

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The Significance of Multiple Node Field Drainage in Patients with Primary Cutaneous Melanoma in the Era of Sentinel Node Biopsy E. Taylor,[1]* L. Haydu,[1] J.R. Stretch,[1] R.F. Uren,[2] R.P. Saw,[1] J.F. Thompson.[1] *1. Melanoma Institute Australia, Sydney, NSW, Australia; 2. University of Sydney, Sydney, NSW, Australia.*

Background It has been suggested that lymphatic drainage to multiple node fields (MNFD) is associated with a worse prognosis in patients with melanoma, but there is conflicting evidence in the literature. The aim of this study was to clarify the significance of MNFD by analyzing a large series of patients managed at a single institution. Methods Patients diagnosed between January 1992 and June 2011 with a single invasive primary melanoma, who had undergone lymphoscintigraphy, were identified from a prospectively maintained database (n=6135). The effects of MNFD on sentinel node (SN) positivity, loco-regional recurrence and survival were assessed. Statistical analysis was performed using IBM SPSS® Statistic 19.0. Results MNFD occurred in 1400 patients (23%). The rate of SN positivity in the MNFD group was similar to the single node field drainage (SNFD) group (16.9% vs. 15.4%; p=0.28). In multivariate analysis, patients with MNFD were at significantly greater risk of loco-regional recurrence (HR=1.21, 95%CI: 1.01-1.45, p=0.04). In the overall cohort, MNFD significantly influenced time to first recurrence, on both univariate and multivariate analyses (HR=1.19, 95%CI: 1.03-1.38, p=0.02). 5Y and 10Y recurrence-free survival for the MNFD group vs. the SNFD group were 69.7% vs. 73.6% and 62.4% vs.66.5% respectively (p=0.01). MNFD significantly influenced time to death from melanoma on univariate analysis (p=0.01), but on multivariate analysis MNFD was no longer a significant prognostic factor. 5Y and 10Y melanoma specific survival for the MNFD group vs. the SNFD group were 81.1% vs. 84.5% and 70.9% vs. 77.4% respectively (p=0.015). Conclusions MNFD is common, particularly in patients with truncal melanoma. Our study indicates that the presence of MNFD is associated with a higher risk of, and decreased time to, loco-regional recurrence. However, MNFD was not associated with an increased likelihood of SN positivity or poorer overall survival.

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International Multi-Institutional Management and Outcome of Patients with Positive Sentinel Lymph Nodes (SLNs) in More than One Nodal Basin L.G. Melstrom,[1]* E. Taylor,[2] D. Kuk,[1] T.L. Frankel,[1] K. Panageas,[1] L. Haydu,[2] M.S. Sabel,[3] J.F. Thompson,[2] C. Ariyan,[1] D.G. Coit,[1] M.S. Brady.[1] *1. Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; 2. Sydney Melanoma Unit, Sydney, NSW, Australia; 3. University of Michigan, Ann Arbor, MI.*

Introduction: In patients with palpable nodal disease, involvement of more than one basin is associated with a worse prognosis than single basin disease. Little is known about the current management or outcome of patients with microscopically positive nodal disease in more than one nodal basin. Patients and Methods: We identified 112 patients with positive SLNs in more than one lymph node basin from 1994-2010 from three tertiary care centers. Patients that presented with metastases or recurrence were excluded, yielding 97 patients for analysis. Clinical and pathologic outcome variables were recorded and analyzed. Results: Ninety-seven patients (72 male, 25 female) were identified with at least one positive SLN in at least two node basins. Most primary lesions were truncal (68, 70%) followed by extremity (16, 16%) and head/neck (13, 13%). The median Breslow depth was 3.2 mm (range 0.8-12) and 49 (51%) were ulcerated. The most frequently involved nodal basins were the axilla (112; 57%), the neck (34, 35%) and the inguinal (24, 25%). The median number of positive SLNs was 2 (range 2-8). Seventy-six (78%) patients underwent completion lymph node dissections (CLND). Sixty eight percent (134/198) of all positive sentinel lymph node basins proceeded to completion lymph node dissection. Twenty-two (29%) patients had additional positive nodes after CLND. After SLN biopsy, the median time to first recurrence was 20 months. The majority of first recurrences were distant (42, 43%), followed by regional non-nodal (17, 18.5%) and regional nodal metastases (16, 17%). At a median follow up of 49 months (range 1-119), 38 (39%) patients have died of disease, 43 (44%) have no evidence of disease and 7 (7%) are alive with disease. Median overall survival was 41 months. There was no significant difference in survival in the CLND vs no CLND groups (49 vs 43 months respectively). Conclusions: Most melanoma patients with positive SLN's in multiple basins are managed with CLND. Outcome in this group is poor, and more effective management strategies than CLND are needed.

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Poor Prognostic Significance of Axillary Nodal Extracapsular Spread in Patients with Stage III Metastatic Melanoma D.W. Ollila,[1]* J.R. Stretch,[2] M.O. Meyers,[1] L.E. Haydu,[2] J.S. Frank,[1] J.F. Thompson.[2] *1. Univ of NC at Chapel Hill, Chapel Hill, NC; 2. Melanoma Institute Australia, North Sydney, NSW, Australia.*

Intro: Recently, the ability of a level I/II/III axillary lymph node dissection (ALND) to control locoregional disease has been questioned (Davis et al., ANZ J Surg 2010). This study aims to quantify the locoregional recurrence (LR) rate and identify risk factors for LR, as well as identify risk factors for melanoma-specific survival following ALND. Methods: Two prospective, ethics-approved melanoma databases were queried for all stage III metastatic melanoma patients, palpable or sentinel node-positive, who then underwent a complete (levels I/II/III) ALND. Statistical analyses were performed on the resulting dataset with IBM SPSS Statistic 19.0. Results: We identified 739 eligible patients with a median age of 56 years. Primary location: 170(23%) upper limb/shoulder, 487(66%) trunk and 82(11%) occult. The median number of nodes removed in the ALND was 22. The axillary LR rate was 10.6% (78/739) with a mean follow-up of 39 months. 172 (23.3%) patients received postoperative radiotherapy and 39 had an axillary LR. Of the demographic, primary tumor and nodal pathologic factors examined, the only predictor of axillary LR following ALND was nodal extracapsular spread (ECS) (HR 1.86 95% CI: 1.10-3.15, p=0.020). In the table, multivariate melanoma-specific survival is reported, with the presence of ECS a very strong poor prognostic factor (HR 1.96, 95% CI: 1.48-2.60, p<0.001). Furthermore, the 5-yr survival for patients with/without axillary nodal ECS was 29.4% v 60.0% (p<0.001). Conclusions: Excellent axillary LR control can be achieved with an ALND. Nodal ECS is a predictor of both LR failure and melanoma-specific mortality. Studies investigating the use of nodal basin irradiation and systemic agents are warranted to improve both LR control and mortality in this high-risk subset.

Multivariate melanoma-specific survival from ALND (n=739)

Factor	Value	HR	95%CI	P-value
Age at ALND (yrs)	Continuous	1.01	1.00-1.02	0.005
Primary Site	Upper limb/shoulder		reference	
	Trunk	1.65	1.19-2.30	0.003
	Occult	1.23	0.77-1.96	0.397
Multiple Primary Melanomas	Multiple	0.54	0.35-0.83	0.005
Nodes Positive on ALND	Continuous	1.09	1.06-1.11	<0.001
Presence of ECS	Present	1.96	1.48-2.60	<0.001

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Outcomes in Patients with Sentinel Node Positive, Palpable and Bulky Axillary Disease from Melanoma C. Nessim,* F. Wright. *Sunnybrook Health Sciences Centre/Odette Cancer Centre, University of Toronto, Toronto, ON, Canada.*

INTRODUCTION Very limited data exists regarding the necessity of resecting level three lymph nodes as part of an axillary dissection, especially for patients with sentinel lymph node disease from melanoma. The objective of this study was to determine how often the level III nodes have melanoma metastases in patients with sentinel node positive, palpable and bulky axillary disease and to determine patient outcomes. METHODS A retrospective chart review was completed at a tertiary care centre of patients with melanoma that had either sentinel node positive, palpable or bulky axillary disease and had a level three axillary dissection with curative intent. All patients had a CT head, chest, abdomen/pelvis as part of a metastatic work up prior to surgery. At the time of surgery, the level III nodes were sent as a separate specimen. Bulky disease was defined as a large mass of matted nodes in all 3 levels such that the surgeon was unable to dissect the level III nodes separately. Clinical and pathologic endpoints were collected and descriptive statistics were calculated. RESULTS 72 patients were identified (mean age 60, 64% male). 56% had T3-4 disease and 11% had an unknown primary. 52% of patients had a positive sentinel node, 38% had palpable disease and 10% had bulky disease. 2.6%, 18.5% and 100% of patients with a positive sentinel node, palpable and bulky disease, respectively, had further disease in their level III nodes. Median follow-up was 37 months and 4% of patients were lost to follow-up. Development of distant metastases occurred in 16%, 78% and 86% of patients with SLN disease, palpable and bulky disease respectively. The time interval between axillary dissection and development of distant metastases for patients with bulky, palpable and SLN disease was 4.3, 9.7 and 8.8 months respectively. CONCLUSION Patients with SLN disease rarely have positive Level III nodes and a Level I/II dissection may be adequate, thus avoiding an unnecessary morbid procedure. In patients with palpable disease the risks and benefits should be weighed in order to provide the patient with appropriate care. These results may guide discussions with patients about their prognosis.

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The Unique Clinical Characteristics of Melanoma Diagnosed in Children D. Han,[1]* S.S. Marzban,[1] G. Han,[2] J.L. Messina,[1] V.K. Sondak,[1] J.S. Zager.[1] *1. Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL; 2. Department of Biostatistics, Moffitt Cancer Center, Tampa, FL.*

Introduction: Studies suggest that melanoma diagnosed in children is associated with higher rates of nodal metastases but better overall survival rates. We herein describe a large single institution experience with pediatric melanoma. Methods: Retrospective review identified 126 patients (pts) diagnosed at age ≤21 years with melanoma from 1982 to 2011 and referred to a single institution for treatment. Clinicopathologic characteristics and outcomes were reviewed. Results: Median age was 18 years and 57.9% of pts were female. Median Breslow thickness was 1.18mm. Ulceration and mitotic rate (MR) ≥1 were seen in 18/126 (14%) and 33/126 (26%) cases respectively. Overall 62/126 (49%) pts had a sentinel lymph node (SLN) biopsy (SLNB) and 18/62 (29%) patients had a +SLN. A +SLN correlated with increasing Breslow thickness (p<0.0001) while ulceration (p=0.055) and MR ≥1 (p=0.084) trended towards significance. Primary tumor characteristics and SLN status based on age groups of <12, ≥12 to <18 and ≥18 to ≤21 years are shown in the Table. In total, 14/18 +SLN pts had a completion lymph node dissection (CLND). In 2/14 (14%) cases, additional positive nodes were found. Of the 4/18 cases without a CLND, 2 pts were lost to follow-up while a CLND was not performed in 2 other pts based on surgeon and patient discussion. Fifteen pts developed isolated regional recurrences. In 10/15 cases, SLNB was not performed while in 2/15 cases,

SLNB was negative. In 3/15 cases, regional recurrences occurred either after a positive SLNB with no CLND (1 case) or after a neck CLND (2 cases). In total, 30/126 (24%) pts developed nodal metastases. After a median follow-up of 5 years, median overall survival (OS) and median recurrence-free survival (RFS) have not been reached however, worse OS and RFS are correlated with increasing Breslow thickness, +SLN status and recurrence of disease ($p<0.05$). Conclusions: Melanoma diagnosed in children behaves in a clinically unique manner with SLN metastases occurring at a higher rate (29%) than historically reported for adults. However, despite the higher rate of nodal metastases, younger pediatric pts (<18 years and especially <12 years) appear to have better survival.

Age group (years)	N	Median Breslow thickness (mm)	Ulceration	Mitotic rate ≥1	+SLN	Recurrence	Died of disease
<12	7	2.00	1	2	1	2	0 (0%)
≥12 - <18	55	1.15	8	13	9	12	5 (9%)
≥18 - ≤21	64	1.15	9	18	8	14	14 (22%)

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Phase I Trial of Neoadjuvant Conformal Radiotherapy plus Sorafenib for Patients with Locally Advanced Soft Tissue Sarcoma of the Extremity R.J. Canter,* D. Borys, A. Olusanya, X. Yang, W. Mak, W. Monsky, S.D. Christensen, R.M. Tamurian, A. Monjazeb. *Surgery/Surgical Oncology, UC Davis Medical Center, Sacramento, CA.*

Introduction: Despite effective local therapy with surgery and radiation (RT), approximately 50% of patients with high grade soft tissue sarcoma (STS) will die of disease. Since experimental data suggest a significant synergistic effect when anti-angiogenic targeted therapies, such as sorafenib, are combined with RT, we chose to evaluate preoperative combined modality sorafenib and conformal RT in a Phase I/II trial among patients with extremity STS amenable to treatment with curative intent. (clinicaltrials.gov #NCT00864032) Methods: Eight patients with intermediate or high grade STS > 5 cm in maximal dimension or low grade STS > 8 cm in maximal dimension received concomitant sorafenib (dose escalation cohort 1:200 bid, cohort 2:200/400 daily, cohort 3:400 bid) and preoperative RT (50.4 Gy in 28 fractions). Sorafenib was continued during the entire period of RT as tolerated. Surgical resection was completed four to six weeks following completion of neoadjuvant sorafenib/RT. Three sorafenib dose levels were planned. Key endpoints of the Phase I were maximal tolerated dose and dose-limiting toxicity (DLT). Results: Eight patients were enrolled in the Phase I (5 female, median age 44, 3 myxoid/round cell liposarcoma, 3 high grade pleomorphic, 2 other). Median tumor size was 16 cm (range 6-26), and all tumors were located in the proximal lower extremity. Two of 5 patients treated at dose level 2 developed DLT consisting of grade 3 rash not tolerating drug reintroduction. Other side effects included perirectal abscess and SVT, both of which occurred while patients were off therapy. Radiation toxicity (grade 1 or 2 dermatitis, N=8) and post-surgical complications (3 grade 3 wound complications) were comparable to historical controls and other series of preoperative RT monotherapy. There were 3 pathologic complete responders (≥ 95% tumor necrosis). Conclusion: Neoadjuvant sorafenib in combination with RT is tolerable and appears to show activity in locally advanced extremity STS. Further study to determine efficacy at dose level 1 is warranted.

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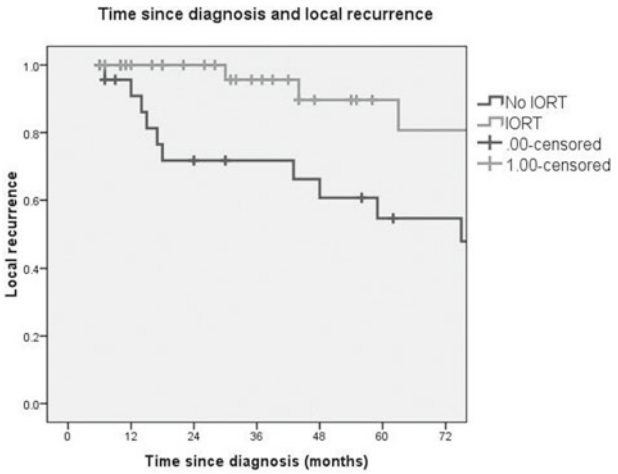
The Combination of Preoperative Radiation Therapy, Surgical Resection, and Intra-operative Radiation Therapy Improves Local Control of Retroperitoneal Sarcoma C.H. Stucky,* N. Wasif, J.B. Ashman, B.A. Pockaj, L.L. Gunderson, R.J. Gray. *Mayo Clinic Arizona, Phoenix, AZ.*

Introduction: Retroperitoneal sarcoma is an uncommon soft-tissue sarcoma with few studies reporting on the value of surgical resection combined with preoperative external beam radiation therapy (EBRT) and intraoperative radiation therapy (IORT). Methods: A retrospective review of 64 consecutive patients treated with surgical resection from 1996-2011 was performed. Results: Thirty-eight patients (59%) underwent EBRT and IORT, two (3%) underwent EBRT, and 24 (38%) had resection without EBRT or IORT. The median age was 66 years and 59% were male. The median tumor size was 10 cm, 53% of tumors were high grade, and 34% of patients had locally recurrent disease. Of the IORT patients, 47% had locally recurrent disease. The most common histological classifications were liposarcoma (66%) and leiomyosarcoma (13%). Final margin status was: R0 72%, R1 6%, R2 16% and unknown 6%. Of the patients with R0 resections, 67% received IORT; for R1 patients, 50%; for R2, 4%, and for unknown, 25%. Median follow-up was 36 months from diagnosis. The five-year local recurrence (LR) rate was 32% for the entire cohort. For IORT patients, the five-year LR rate was 19% versus 48% for non-IORT patients ($p=0.002$, Figure). The median time to LR was 29 months with IORT and 12 months without IORT ($p=0.008$). On univariate analysis, IORT, EBRT, R0 resection, and early stage were associated with a lower risk of LR. On multivariate analysis, IORT was the only variable associated with a lower risk of LR (OR 7.9 for LR with no IORT; CI 2.0-31.4, $p=0.003$). Five-year overall survival (OS) was 62%. The OS at two and five years was 76% and 62%, respectively for IORT patients and 72% and 62%, respectively for non-IORT patients ($p=0.26$). Conclusions: The combination of pre-operative EBRT, surgical resection, and IORT reduces the risk of local recurrence compared to resection without IORT for retroperitoneal sarcoma. IORT prolongs the disease-free interval for those patients who locally recur but does not impact overall survival in this study.



Local Recurrence Rates in Patients Undergoing IORT versus non-IORT Patients.

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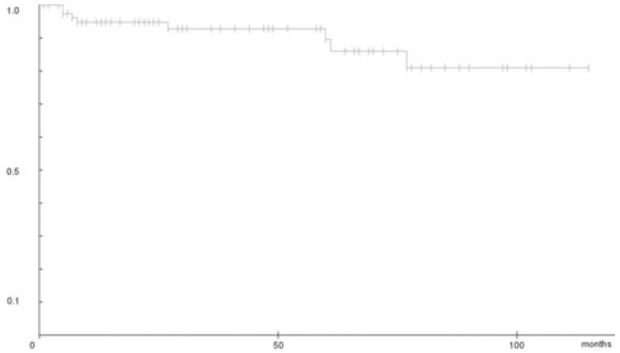
Clinical, Pathological and Surgical Characteristics of Duodenal Gastrointestinal Stromal Tumor and Their Influence on Survival: A Multi-centre Study C. Colombo,[1] U. Ronellenfitsch,[2]* Y. Zhong,[3] P. Rutkowski,[4] C.P. Raut,[3] P. Hohenberger,[2] A. Gronchi.[1] *1. National Tumor Institute, Milan, Italy; 2. Surgical Oncology and Thoracic Surgery, University Medical Center Mannheim, Mannheim, Germany; 3. Dana-Farber/Harvard Cancer Center, Boston, MA; 4. Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warszaw, Poland.*

INTRODUCTION: The duodenum is a rare site of primary gastrointestinal stromal tumor (GIST). There is an ongoing debate regarding the most appropriate surgical and multimodal therapy for duodenal GIST. This multi-center study assesses how clinical and pathological features influence overall (OS) and recurrence-free survival (RFS) of patients (pts) with primary duodenal GIST. METHODS: All patients who underwent surgery for primary non-metastatic duodenal GIST between 2000 and 2010 were reviewed from prospective institutional databases at four high volume sarcoma centers in four countries. Median follow-up was 36 months. RESULTS: 79 pts were identified (52% male; median age 56 [range 27-75] yrs). Mutational data was available for 32 pts: c-KIT exon 11 (14 pts), c-KIT exon 9 (7), wildtype (7), PDGFRA D842V (2), and other (2). 53 pts (67%) underwent limited resection (LR) and 26 pts (33%) pancreaticoduodenotomy (PD). Imatinib (IM) was given preoperatively in 11 pts (13.9%) and postoperatively in 12 pts (15.2%). Tumors were larger in the PD than the LR group (median 9 vs 5

cm, p=0.03). 12 pts (15%) developed only abdominal recurrence, 19 pts (24%) only liver metastases, 17 pts both (21%). For the entire cohort, median OS was not reached (see figure), and median RFS was 52 months. Median RFS was not reached for pts with LR and 32 months for pts with PD (log-rank test: p=0.07). Multivariate Cox regression analysis did not show significant correlation between OS and age, sex, pre- or postoperative IM, mutation, mitotic count, or type of surgery. In the analysis for RFS, there was significant correlation with mitotic count (p<0.01) and mutation (p=0.05). CONCLUSIONS: Duodenal GISTs are a challenging entity. Surgical treatment should be guided by clinical presentation. Preoperative IM treatment is a viable option to decrease tumor size and potentially facilitate organ-sparing resection. It needs to take into account molecular biology as some primary duodenal GISTs harbor mutations which are IM resistant or require a higher dose. RFS is determined mostly by pathological factors such as mitotic count and mutational status.



Kaplan-Meier curve for overall survival of all 79 pts

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Risk of Recurrence after Surgical Treatment for Extra-abdominal Aggressive Fibromatosis D. Van Broekhoven,[1]* T. Van Dalen,[2] A.J. Witkamp,[1] K. Verhoef,[3] J. Van Gorp,[2] B.N. Van Geel,[3] H.K. Wijrdeman.[1] *1. University Medical Center, Utrecht, Netherlands; 2. Diakonessenhuis, Utrecht, Netherlands; 3. Daniel den Hoed Cancer Clinic, ErasmusMC, Rotterdam, Netherlands.*

Extra-abdominal aggressive fibromatosis (desmoid tumors) are benign soft tissue tumors with a biological behavior which varies between relatively indolent and progressive growth. The reported frequency of local recurrence in 5 years after treatment ranges from 5% up to 63%. Although there is a trend to treat desmoid tumors more conservatively, surgery remains the standard treatment for these locally aggressive tumors. Data was collected between November 1989 and May 2011 from 3 hospitals in the Netherlands. 152 patients were diagnosed with an extra-abdominal desmoid tumor. In the selection of patients that underwent surgical resection for a primary tumor, the risk of local recurrence was assessed and possible influencing factors evaluated. Median follow-up was 39 months (range 1-222 months). Overall, 140 patients (92%) received surgical treatment for a primary tumor. The average age was 37 years (range 1-80 yr.) and the majority was female (62%). Macroscopic residual tumor remained for 6 patients (4%). Based on pathological examination, a microscopic radical resection (R0) was achieved in 91 patients (65%) while 38 patients (27%) had microscopically involved margins (R1). For 5 patients, the surgical margin was unknown. In addition to surgery, 60 patients (43%) received adjuvant radiotherapy. The 5-year cumulative risk of local recurrence was 18% with a median time to recurrence of 18 months. Both univariate and multivariate analysis showed no significant influence of tumor size, R0 vs R1 resection, or radiotherapy on the risk of local recurrence. Conclusion: After surgical treatment of an extra-abdominal aggressive fibromatosis, the 5-year risk of local recurrence was low. Since microscopic irradical resection and radiotherapy did not influence local recurrence rate, the necessity of aggressive local treatment may be questioned.

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Impact of R0 Resection and Tumor Site on Recurrence after Surgery for Aggressive Fibromatosis: A Single-Centre Experience over 15 Years E. Bertani,[1]* A. Chiappa,[1] A. Testori,[2] P. Misitano,[1] T. De Pas,[3] G. Viale,[4] B. Andreoni.[1] *1. General and Laparoscopic Surgery, European institute of Oncology, Milan, Italy; 2. European Institute of Oncology - Division of Melanoma and Muscolo-cutaneous Sarcoma, Milan, Italy; 3. European Institute of Oncology - Division of Medical Oncology, Milan, Italy; 4. European Institute of Oncology - Division of Pathology, Milan, Italy.*

Background: Surgery is still the standard treatment for aggressive fibromatosis (AF), however local control remains a significant problem and the significance of R0 surgery and its impact on recurrence-free survival (RFS) is a matter of contradictory reports. Methods: This is a single-Institution study of 62 consecutively patients affected by AF who received macroscopically radical surgery within a time period of 15 years. Surgical principles that aided resection comprised a wide excision of the mass which involved the removal of all gross disease together with a normal tissue rim of at least 1 cm whenever possible, with the aid of intraoperative frozen section (IFS) margin evaluation in some cases. Results: The disease was primary in 52 and recurrent in 10 patients. The tumor was confined to trunk in 42, head and neck in 7, limbs in 7 and mesentery in 6 patients. The definitive pathology examination confirmed an R0 situation in 49 patients and R1 in 13 patients. The 17 patients who had IFS margin evaluation had a significantly higher probability of receiving R0 surgery (17 of 17 vs 32 of 45, p=0.013). Five-years RFS for patients who underwent R0 vs R1 surgery was 93% vs 54% (p=0.039), for tumor diameter <10 vs ≥10 cm 92% vs 65% (p=0.038) and for limb vs other localizations 68% vs 90% (p=0.013) respectively. Age, gender, tumor presentation (primary vs recurrent) did not impact RFS. Patients who had IFS margin evaluation showed a significantly better RFS in comparison with patients who did not have such assessment (5-years RFS 100% vs 81%, respectively, p=0.049). In multivariate analysis only limb localization showed a negative impact on RFS (HR: 1.708, 95% CI 1.03 to 2.84, p=0.039). Conclusions: IFS evaluation should be a staple of desmoid treatment in order to define proper R0 surgery. Non-surgical treatment including watchful follow-up could be indicated for patients with limb AF localization, because of the high risk of recurrence even after R0 surgery.

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Timing of Surgery and the Role of Adjuvant Radiation Therapy in Ewing Sarcoma of the Chest Wall: A Single Pediatric Institution Experience J.W. Denbo,* W. Orr, Y. Wu, J. Wu, C.A. Billups, F. Navid, B. Rao, A.M. Davidoff, M.J. Krasin. *St. Jude Children's Research Hospital, Memphis, TN.*

Ewing sarcoma (ES) is the most common chest wall malignancy in adolescents. Current treatment strategies incorporate chemotherapy to treat systemic disease and ionizing radiation to assist with local control. We sought to evaluate the timing of surgery and the role of adjuvant radiation therapy in the management of these tumors. We reviewed our institutional experience in treating children with ES of the chest wall from 1979-2009. Patient demographics, tumor characteristics, treatment variables, and outcomes were recorded and analyzed with respect to the timing of surgical resection and use of adjuvant radiation. Thirty-six patients with ES of the chest wall were included in our review. At diagnosis, the mean tumor size was 10 cm; 39% had evidence of metastatic disease. With a median follow-up of 14 years, the 15-year estimates of event-free survival (EFS) and overall survival (OS) were 56% ± 11% and 66% ± 11%, respectively. The timing of surgical resection (up-front vs. delayed) in patients with localized disease did not appear to impact the rate of margin negativity or the use of adjuvant radiation, but did decrease the extent of chest wall resection. Additionally, 36% of patients who received neoadjuvant chemotherapy were found to have a complete pathologic response. When considering radiation, we found that patients with localized disease who did not receive adjuvant radiation therapy had smaller tumors (p=0.04) and were more likely to have had negative margins (p=0.03). The 15-year estimates of OS were 74% for those who received adjuvant radiation and 100% for those who did not receive radiation. Multimodal therapy for ES of the chest wall yields good long-term results. Delayed surgical resection may or may not improve rates of margin negativity which directly impacts the use of adjuvant radiation, but does decrease the extent of chest wall resection and helps define a patient population with favorable tumor biology. In addition to patients with

complete pathologic responses to chemotherapy, those with tumors < 8 cm and negative surgical margins may be spared adjuvant radiation without any decrement in OS.

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Prognostic Importance of Etiology in Malignant Peripheral Nerve Sheath Tumors J. LaFemina,* L. Qin, C.R. Antonescu, N.H. Moraco, R.C. Fields, A.M. Crago, M.F. Brennan, S. Singer. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction. Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive soft tissue sarcomas that occur sporadically, with prior radiation therapy (RT), or in association with neurofibromatosis type 1 (NF1; lifetime incidence 8-13%). Two recent studies suggested that patients with NF1-associated MPNST have a worse outcome than those with sporadic MPNST, but this remains controversial. The goal of this study was to determine the prognostic impact of sporadic, NF1-associated, and RT-induced MPNST. Methods. From July 1982 to June 2006, patients with primary high-grade MPNST were identified from a prospectively maintained database. Patients with sporadic MPNST were included only if the MPNST was associated with a neurofibroma or was positive for S100 immunohistochemistry and in the absence of a diagnosis or stigmata of NF1. Results. We studied 105 patients; 42 had tumors associated with NF1, 49 sporadic, and 14 RT-induced. The median age at diagnosis was 38 yr. Median follow-up for surviving patients was 4 yr. Mean tumor size was 9.1 cm overall and 5.5 cm for RT-induced MPNST, which was significantly less than the 9.7 cm for NF1 and sporadic tumors (P<0.001). Multivariate analysis demonstrated that the factors associated with worse DSS were larger size (hazard ratio [HR] 1.08; 95% confidence interval [CI] 1.04-1.13; P<0.001) and positive margin (HR 3.30; 95% CI 1.74-6.28; P<0.001). Age, gender, site of disease, and S100 staining were not associated with DSS. Three-year and median DSS did not differ significantly for NF1 and sporadic cases; combined 3-year DSS was 64% and median DSS was 8.0 years. For RT-induced tumors, 3-year DSS was 49% and median DSS was 2.4 years (Table 1). The relationship between RT-associated tumors and worse DSS approached statistical significance (HR 2.29; 95% CI 0.93-5.67; P=0.072). Conclusions. Margin status and size continue to be the most important predictors of DSS in patients with MPNST. RT-induced MPNST may be associated with a reduction in DSS compared to sporadic and NF-1 associated MPNST. Discovery of the genetic alterations driving their more aggressive clinical behavior may help identify new targets for therapy.

Differences in demographics and oncologic outcomes in MPNST, by subtype

	NF-1 Associated and Sporadic (N=91)	RT-Induced (N=14)
Age, median (yr)	37.1	49.5
Maximum diameter, mean ± SEM (cm)	9.7 ± 0.8	5.5 ± 0.8
Median DSS (yr)	8.0	2.4
3-year DSS (%)	64	49

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Understanding the Molecular and Genetic Alterations Associated with Malignant Peripheral Nerve Sheath Tumors E. Shurell,[1]* J. Nakashima,[1] K.B. Smith,[1] L. Tran,[1] W.D. Tap,[2] S.M. Dry,[1] H. Wu,[1] F.C. Eilber.[1] *1. University of California - Los Angeles, Los Angeles, CA; 2. Memorial Sloan-Kettering Cancer Center, New York City, NY.*

INTRODUCTION: Malignant peripheral nerve sheath tumors (MPNSTs) are the sixth most common type of soft tissue sarcoma with a five-year disease specific mortality of up to 70%. MPNSTs occur in patients with neurofibromatosis type 1 (NF1) or can occur spontaneously in the general population. Currently, there is no effective therapy due to our very limited understanding on the major pathway alterations associated with MPNST development. The aim of this study is to take an unbiased approach to evaluate key genetic and pathway alterations associated with sporadic and NF-1-associated MPNST patient populations. METHODS: A retrospective review of all patients with MPNSTs (n = 135) from our sarcoma database (1974 - 2011) was performed, including pathology associated with their surgical resected tissues. MPNST patients were then grouped into spontaneous and NF-1-associated MPNST and further subgrouped by age, gender, grade and location of the disease. Eight NF1-associated and seven spontaneous MPNST samples have been profiled using Affymatrix SNP and mRNA arrays. As non-malignant controls, we also profiled two peripheral nerves, 11 schwannomas and 7 neurofibroma samples. RESULTS: We found both differential and overlapping genetic alterations associated with these two types of MPNST malignancies, which are not present in either benign schwannoma or neurofibroma lesions. Among these alterations, PTEN copy number variation (CNV) happens significantly higher in spontaneous MPNSTs (43%) than in NF1-associated MPNSTs (25%), while NF1 (ch 17) deletion occur at similar frequencies in both spontaneous and NF1-associated MPNSTs. Our study also identified several novel genetic alterations specifically associated with spontaneous MPNSTs. When using gene expression changes as functional readouts for CNVs, we further narrowed down these spontaneous MPNST associated genomic changes to 1q, 8q, 19qq, 20q, and 22q amplifications and 9p and 11q deletion. CONCLUSIONS: Unbiased genomic and transcription analyses will help in determining major alterations associated with MPNST malignancies and identifying potential treatment target.

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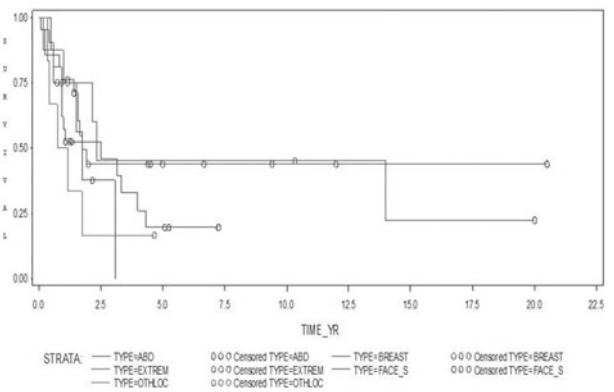
Challenges in Treatment of Angiosarcoma: A Single Institution Experience S. Singla,[1]* P. Papavasiliou,[2] B. Powers,[1] J. Gaughan,[1] M. Von Mehren,[2] J.C. Watson,[2] J.M. Farma.[2] *1. Temple University Hospital, Philadelphia, PA; 2. Fox Chase Cancer Center, Philadelphia, PA.*

INTRODUCTION: Angiosarcoma is a rare multi-focal sarcoma that carries a poor prognosis. Due to its nature of insidious growth, initial diagnosis is often difficult and delayed. The objective of this study is to determine the long-term outcome of patients with angiosarcoma at our institute. METHODS: Between 1990 and 2011, 72 patients diagnosed with angiosarcoma were treated at our institution. Pathologic confirmation was obtained for all cases prior to inclusion. Multiple prognostic factors were evaluated for disease-specific survival. Survival analysis was based on the Kaplan-Meier method with log-rank test and univariate Cox regression with statistical significance set at < 0.05. RESULTS: Seventy-two patients (41: F, 31: M, mean age 62 years) were identified for our analysis. Of these, 28 cases were sporadic and 44 cases were secondary angiosarcomas. Amongst secondary, 23 patients (52 %) had prior exposure to radiation, 16 (36 %) patients had overexposure to sun, and 2 (4.5 %) patients each had vascular malformation and lymphedema while one patient (2 %) had exposure to a carcinogenic chemical. The latent period between radiation exposure and diagnosis was predictive of survival (P=0.037). Presentation was delayed by more than 3 months in 41 % patients; majority of males developed tumors of the head & neck region (n = 15, 48.5 %), while females developed angiosarcoma of the breast (n = 21, 51 %). Metastatic disease was seen in 12 patients at initial presentation. Initial management with surgery (n=43, P=0.005) and subsequent adjuvant chemotherapy (n=14, P=0.0183) were significant predictors of overall survival. Most patients developed recurrence (mean 27 months, range 4 -108 months) and required a second modality of treatment. The mean survival time was 62 months (range, 1–246 months), however in patients who underwent surgery, the mean survival time was 84 months in our patient cohort. CONCLUSIONS: Angiosarcoma is a rare aggressive tumor with the majority arising from secondary exposure to sun or radiation. Diagnosis if often delayed, which may affect survival. Clinical suspicion and prompt diagnosis are quintessential in initiating multimodal therapy leading to improved survival.



Overall survival in patients with angiosarcoma

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Analysis of Radiation-associated Angiosarcoma of the Breast K.E. Torres,* K. Kin, G. Lahat, B. Arun, K. Hunt, R. Pollock, D. Lev. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: While not common, radiation-associated sarcoma is a devastating late complication of cancer treatment. Due to the rarity of these tumors, knowledge of disease risk factors, epidemiology, treatment, and outcome is extremely limited. This study reports on a cohort of women afflicted by this aggressive disease. METHODS: Radiation-associated-angiosarcomas were defined as pathologically confirmed angiosarcomas arising within a previously irradiated field. Between 1/1990 and 9/2011, patients were identified through a comprehensive search of our institutional tumor registry. A comprehensive retrospective chart review was conducted and a database was constructed to include clinical and pathologic variables in addition to outcomes. RESULTS: 99 female patients were identified, 96 (97%) initially received radiation for breast cancer (stage 0-4.0%, I-37.4% IIA–17.2%, IIB–10%, III-2% and unknown-26.3%) and 3 (3%) for lymphoma. Median follow up time was 2 years (0-11 yrs). There were 61 individuals (62%) that had first degree relatives with a history of cancer. Of four patients for whom germline BRCA status was available, three were positive for BRCA1 mutations and one patient was found to harbor a p53 germline mutation. Breast (n=68), chest wall (n=19) and upper extremity (n=12) angiosarcoma was diagnosed at a median of 7 years (1-21yrs) following radiotherapy. 92 (93%) lesions involved the skin and 7(7%) were in the breast parenchyma; median size was 6cm, and 60(64%) were multifocal. All patients with metastatic disease were treated with chemotherapy. Surgical resection was the major treatment modality for patients with localized disease. The 1- and 5-year disease-specific survival rates were 82% and 32%, respectively. CONCLUSIONS: Radiation-associated sarcoma is an aggressive and highly fatal complication of cancer treatment with radiation therapy. The identification of molecular risk factors that may predispose patients to radiation-associated sarcoma development is critical and could potentially revolutionize current management guidelines. Expanding initial insights provided here, such as the potential relevance of BRCA1 and/or p53 germline mutations, as molecular predictors should be considered.

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A Single Institution Experience with the Use of Isolated Limb Infusion for Limb Salvage in Extremity Sarcomas N.A. Vohra,[1]* R.J. Gonzalez,[1] K.K. Turaga,[2] A.P. Conley,[1] D.R. Reed,[1] D. Cheong,[1] D.G. Letson,[1] J.S. Zager.[1] *1. Moffitt Cancer Center and Research Institute, Tampa, FL; 2. Medical College of Wisconsin, Milwaukee, WI.*

Objective: Locally advanced, maximally treated, limb threatening soft tissue sarcomas (STS) of the extremity pose a significant treatment challenge. We report our experience using isolated limb infusion (ILI) in patients(pts) with STS of the extremities. Methods: 18 pts with STS underwent 22 ILIs with melphalan and dactinomycin from 2008 to 2011. Outcome measures included limb-salvage rates and in-field response rates. Toxicity was measured using the Wieberdink (WBD) scale and serum creatinine phosphokinase (CK) levels. Results: Median age was 71 years. 12 pts (67%) were women. Sarcoma subtype histology was as follows: 8 (44 %) malignant fibrous histiocytoma, 2 (11%) Kaposis, 2 (11%) synovial sarcoma, 1 each (6% each) had epithelioid, leiomyosarcoma, myxoinflammatory fibroblastic, angiosarcoma, myxofibrosarcoma and undifferentiated sarcoma. 18 ILIs were performed for lower extremity (LE) and 4 for upper extremity (UE) STS. 4 pts had repeat ILI. ILI was aborted in 1 patient due to positionally occlusive brachial artery who then had an above elbow amputation. Median length of stay was 6 days. Procedure was well tolerated with WBD grade III toxicity or less in all pts. Median peak CK levels were 607 and 69 U/L for LE and UE ILI respectively. Median follow up was 13 months (mo). 14 pts were evaluable at 3 mo post ILI. Of the pts that had a single ILI, 2(14%) had a complete response (CR), 4 (29%) a partial response (PR), 1 (7%) stable disease (SD) and 7 (50%) progressive disease (PD). Of the 4 pts having redo ILI, there was 1 (25%) each with a CR, PR, SD and PD. 14 of the 18 pts (78%) in the intent to treat population underwent successful limb preservation at a median of 18 mo. 2(11%) pts were downstaged to resectable disease post ILI, were successfully resected for NED and remain NED at 22 and 12 mo post ILI. Conclusion: ILI is an attractive modality that provides regional control and limb preservation in majority of pts with locally advanced, limb threatening extremity sarcoma. Although short term results appear encouraging, long term follow is needed to fully assess the role of ILI in unresectable STS of the extremities.

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Regionalization and Outcomes of Hepatopancreaticobiliary Cancer Surgery in the United States, Analysis of the Nationwide Inpatient Sample P.D. Colavita,* V.B. Tsirline, I. Belyansky, R.Z. Swan, A.L. Walters, A.E. Lincourt, D.A. Iannitti, B.T. Heniford. *General Surgery, Carolinas Medical Center, Charlotte, NC.*

Background: Recent publications have shown centralization of certain operations to high volume centers (HVCs) in the US. We hypothesize this pattern applies to hepatopancreaticobiliary resections for cancer and has led to improved outcomes. Methods: The Nationwide Inpatient Sample (NIS) data were analyzed from 1995-99 (T1) and 2005-09 (T2) for all hepatic, pancreatic, and biliary cancer resections, using ICD-9-CM codes. Survey-weighted division of hospitals into high-, mid-, and low-volume centers (HVC, MVC, LVC) was performed based on annual resection volume. Socio-demographic factors were examined as effectors of surgery location. Multivariate logistic regression was utilized to control for confounding variables in determining the likelihood of resection at a LVC. Outcomes (death, length of stay(LOS), and total charges) were compared in both eras. Results: A total of 35,502 cases met inclusion criteria (14,316 from T1, and 21,186 from T2). At T1, 31.3% of all resections were performed at HVCs, while 42.2% were done at LVCs. At T2, 60.6% were performed at HVCs vs 18.4% at LVCs. The odds ratio of having a resection at a LVC in T1 vs. T2 is 3.268 ($p < 0.0001$). In multivariate analysis, noncaucasian race (OR 1.27, $p=0.037$), emergent admission (OR 2.55, $p<0.0001$), older age ($p<0.0001$), and female gender (OR 1.28, $p<0.0001$) were independent predictors of resection at a LVC in T1. In T2, independent predictors of resection at a LVC were emergent admission (OR 4.12, $p<0.0001$), older age ($p=0.0044$), female gender (OR 1.31, $p<0.0001$), and private insurance (OR 1.27, $p=0.0178$). In T1, inpatient mortality at HVCs vs. LVCs was 3.3% vs 8.7% ($p<0.0001$), and 2.7% vs. 5.6% ($p<0.0001$) in T2. LOS was also significantly shorter in HVCs vs LVCs in T1 and T2. Conclusion: The most recent NIS data demonstrate better outcomes in HVCs for pancreatic, hepatic, and biliary resections. Trends from 1995-1999 to 2005-2009 reflect alignment with national recommendations to centralize complex cancer surgery, as well as improved outcomes in all centers. Discrepancies in access to HVCs may warrant further investigation.

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A Deviation Based Cost Modeling Analysis of Laparoscopic Versus Open Liver Resection R.M. Cannon, C.R. Scoggins, G. Callender, A. Quillo, K.M. McMasters, R.C. Martin.* *Surgery, Division of Surgical Oncology, Univ Louisville, Louisville, KY.*

Introduction: As laparoscopic hepatectomy has gained acceptance, there is a growing body of literature suggesting equivalent or superior outcomes to open resection. Whether these advances come at an increased financial cost; however, has yet to be adequately determined. The aim of this study was to evaluate the cost and peri-operative outcomes of patients undergoing laparoscopic hepatectomy versus patients undergoing open hepatectomy matched for equivalent pre-operative characteristics. Methods: An evaluation of our 1879 pts HPB database identifying pts who under laparoscopic and open liver resection from 1/1/2005 through 5/31/2011 was performed. Deviation based cost modeling was performed to compare clinical and financial outcomes between the open and laparoscopic group. An "on course" hospitalization was defined as length of stay(LOS) < median for the whole cohort and complications of grade 2 or less. Continuous and categorical variables were analyzed using Student's t-test or chi-squared, where appropriate. Results: There were 160(28%) patients in the laparoscopic and 420(72%) patients in the open resection cohort. The groups were statistically similar in terms of patient and tumor characteristics, as well as operative procedure (table). Patients in the laparoscopic group had fewer complications (18.2% vs. 43.2%; $p=0.009$) and a shorter LOS (mean 4.2 vs. 6.4 days; $p=0.009$). There were no deaths in either group. Patients in the laparoscopic group were significantly likely to be "on course" compared to patients in the open group (73.7% vs 26.8%; $p<0.0001$). Weighted average median total hospital charge in the laparoscopic group was less at $54,801 vs. $69,728 in the open group, since a majority of the laparoscopic liver patients remained "on course" during their hospitalization. Conclusion: Patients undergoing laparoscopic liver resection are significantly more likely to have an "on course" uncomplicated postoperative hospitalization than patients undergoing open resection, with resultant cost savings that average to $14,927 per liver resection.

Laparscopic versus Open Hepatectomy: Cost Comparison

	Age	# Tumors	Tumor Size (cm)	Malignancy (5)	Lobar Resection	Right Posterior	Left Lateral	Non-Weighted Total Charges
Open	58	2	7	81%	73%	2.4%	12%	$67,137
Laparoscopi	61	2	6	74%	54%	12%	30%	$73,542
P-Vaule	0.4	0.5	0.2	0.4	0.06	0.06	0.06	ns

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Description and Predictors of Adverse Events following Ablation Therapy for Hepatic Tumors J. Gustafson,[1]* J. Fox,[1] M. Desai,[2] M. Hellan,[1] T. Thambi-Pillai,[3] J. Ouellette.[1] *1. Wright State University, Dayton, OH; 2. Yale University, New Haven, CT; 3. Sanford School of Medicine, University of South Dakota, Sioux Falls, SD.*

Introduction: Radiofrequency ablation (RFA) for the treatment of hepatic tumors has been increasingly utilized across the United States. Whether treatment-related morbidity has remained low with broader adoption is unclear. We conducted this study to describe in-hospital morbidity associated with RFA for hepatic tumors and to identify predictors of adverse events in a nationally representative database. Methods: Using the 2006-2009 Nationwide Inpatient Sample, we evaluated all patients aged > 40 years who underwent an elective RFA for primary or metastatic liver tumors (n=6,500). Outcomes included in-hospital procedure-specific and post-operative complications. Multivariable logistic regression analyses were performed to identify patient and facility predictors of complications. Results: Most patients underwent a percutaneous (39.9%) or laparoscopic (22.0%) procedure for metastatic liver tumors (57.5%). Procedure-specific complications were frequent (18.2%), with transfusion requirements (10.7%), intra-operative bleeding (4.3%), and hepatic failure (2.8%) the most common. Arrhythmias (AOR=1.93 [1.23-3.04]), coagulopathy (AOR=4.65 [2.95-7.34]), and an open surgical approach (AOR=2.77 [1.75-4.36]) were associated with an increased likelihood of procedure-specific complications, while hospital RFA volume >16/year was associated with a reduced likelihood (AOR=0.59 [0.38-0.91]). Post-operative complications were also common (12.0%) with arrhythmias, heart failure, coagulopathy, and the surgical approach acting as significant predictors. Conclusions: In-hospital morbidity is common following RFA for hepatic tumors. While several patient factors are associated with more frequent procedure-specific complications, treatment at hospitals with an annual volume >16 cases/year was associated with a 41% reduction in the odds of procedure-specific complications.

Predictors of procedure-specific complications

	Complications	AOR	95% CI
Annual RFA Volume			
1-5	24.1%	Reference	Reference
6-15	19.7%	0.76	0.50-1.16
16+	15.7%	0.59	0.38-0.91
Arrhythmia			
No	17.1%	Reference	Reference
Yes	28.8%	1.93	1.23-3.04
Coagulopathy			
No	16.2%	Reference	Reference
Yes	43.3%	4.65	2.95-7.34
Approach			
Laparoscopic	13.4%	Reference	Reference
Percutaneous	16.5%	1.09	0.67-1.76
Unpsecified	15.2%	1.16	0.62-2.15
Open	28.5%	2.77	1.75-4.36

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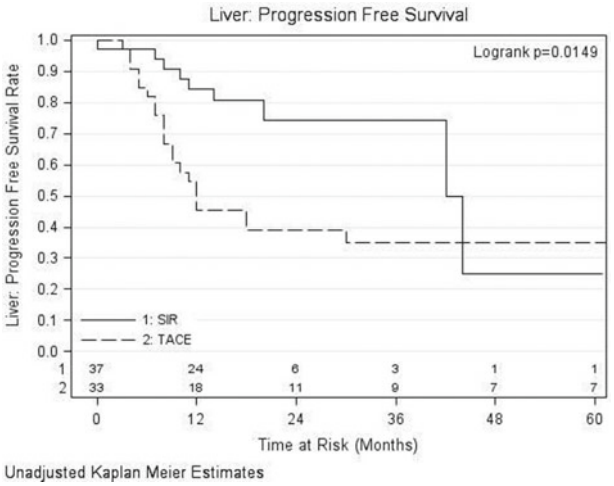
Comparison of Yttrium-90 Microspheres (Y-90) and Transarterial Chemoembolization (TACE) in the Treatment of Inoperable Metastatic Neuroendocrine Tumors (NETS) Y.V. Wu,* G. Tomaszewski, A. Groman, R. Iyer, B. Kuvshinoff. *Roswell Park Cancer Institute, Buffalo, NY.*

INTRO: There are limited modalities to treat inoperable liver NET metastases. This study compares the efficacy and safety of liver-directed yttrium-90 microspheres, SIR-spheres©, to TACE. METHODS: Medical records and axial imaging studies were retrospectively reviewed for all patients with NET liver metastases who underwent SIR or adriamycin based TACE at our institution from Jan 2001 to Dec 2010. The demographics, immediate effects, and time to radiologic progression were assessed and compared between the two treatment modalities. RESULTS: A total of 99 liver directed treatments were performed on 46 pts (n=19 Y-90, n=27 TACE). Median post-treatment follow-up was 20 months (range 4-103 mon). Pt characteristics including age, performance status, type of primary NET, and systemic therapy were similar in both groups. Pts in the SIR group waited longer from the time of metastatic diagnosis to liver-directed therapy (SIR 35 mon vs. TACE 15 mon (p=0.0015)). SIR patients had less liver burden (65% with <25% liver burden) than TACE patients (23% with <25% liver burden). Immediate treatment response (1-3 mon) was measured radiologically using WHO criteria multiplied by EASL criteria. SIR pts achieved 26% complete response (CR), 51% partial response (PR), 15% stable disease (SD), and 8% progressive disease (PR). TACE pts achieved 13% CR, 59% PR, 8% SD, and 21% PD. SIR (44 mon) had a longer radiologic effect than TACE (12 mon) (p=0.015). SIR patients underwent less treatments (95% with < 2 treatments) than TACE patients (70% with < 2 treatments) (p=0.045). Both treatments were well tolerated with minimal side effects. With only 11/46 (25%) deaths, there was no statistically significant difference in overall survival between the two groups with a median follow up of 104 months (range 12-267). CONCLUSION: Liver metastasis from NETs can be successfully treated with yttrium-90 radioembolization. Earlier intervention using SIR allows fewer treatments with more durable responses. Prospective studies controlling for rate of disease progression and disease burden are needed to validate these findings.



Unadjusted Kaplan Meier Estimates

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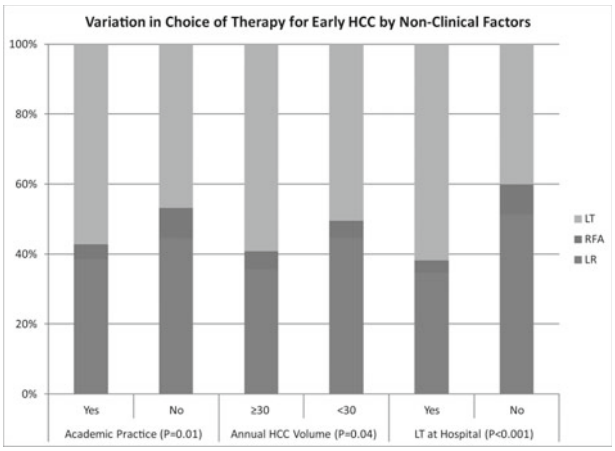
Influence of Non-Clinical Factors on Choice of Therapy for Early Hepatocellular Carcinoma H. Nathan,[1]* J.F. Bridges,[2] M.A. Choti,[1] D.L. Segev,[1] C.L. Wolfgang,[1] B.H. Edil,[1] K. Hirose,[1] A.M. Cameron,[1] R.D. Schulick,[1] T.M. Pawlik.[1] *1. The Johns Hopkins University School of Medicine, Baltimore, MD; 2. The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

Introduction: Initial therapy for early (Milan-criteria) hepatocellular carcinoma (E-HCC) in well-compensated cirrhosis is controversial. While we previously reported on the effect of clinical factors and surgeon specialty, other non-clinical factors may also impact decision-making. We sought to define the influence of these surgeon- and institutional-related factors on choice of therapy for E-HCC. Methods: A web-based survey was used to present HCC case scenarios that varied clinical factors: age, tumor number/size, future liver remnant, cirrhosis etiology, MELD, platelet count, & liver transplant (LT) wait time. Surgeons were asked to choose among initial treatment options for each case: liver resection (LR), radiofrequency ablation (RFA), or LT. Data were analyzed using multinomial logistic regression, yielding relative risk ratios (RRR). Results: There were 336 responses for analysis. Median time in practice was 10 years. Prior surgical training varied: 26% surgical oncology, 43% hepatobiliary, 64% LT. Most respondents were in academic centers (86%) that offered LT (71%). The median number of patients annually evaluated for HCC was 30; median annual HCC procedure volumes were 5 LR, 5 RFA, and 10 LT. Surgeon years in practice had no effect on choice of therapy (P=0.2). Academic surgeons were less likely to choose RFA vs. LT (RRR 0.41, P=0.01) compared with community surgeons, even after adjusting for the influence of

clinical factors. Higher HCC case volume (≥30 vs <30) was associated with a propensity to choose LT over LR (RRR 1.5, P = 0.04). These associations did not persist, however, independent of surgeon specialty. Surgeons who worked at hospitals where LT was performed were much more likely to choose LT over LR and RFA (RRR 2.3 and RRR 3.8, P<0.001), an effect that persisted independent of specialty and among surgeons who do not personally perform LT (RRR 1.3 and RRR 3.3, P<0.001). Conclusions: Surgeon and institution-related factors impact choice of therapy in E-HCC even after adjustment for differences in clinical presentation. These data suggest that choice of therapy for patients with E-HCC varies across medical centers independent of case selection.



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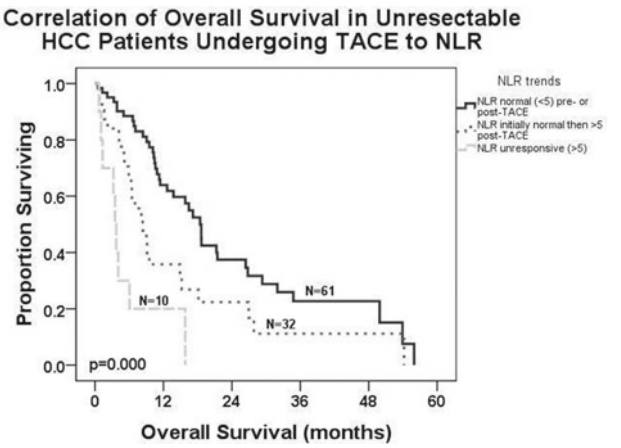
Inflammatory Markers are Associated with Outcome in Patients with Unresectable Hepatocellular Carcinoma (HCC) undergoing Transarterial Chemoembolization (TACE) M.E. McNally,[1]* A. Martinez,[2] L. Malhotra,[1] M. Bloomston,[1] C.R. Schmidt.[1] *1. General Surgery, The Ohio State University- The James Cancer Hospital and Solove Research Institute, Columbus, OH; 2. The Ohio State University Medical Center, Columbus, OH.*

Introduction The serum neutrophil-lymphocyte ratio (NLR) is associated with outcome in several solid organ cancers including hepatocellular carcinoma (HCC). Methods We reviewed our experience in patients with HCC who underwent transarterial chemoembolization (TACE) as the initial treatment over the past 10 years. Serum complete blood counts were used to calculate the NLR prior to and after TACE. The Kaplan Meier method was used to determine survival and significance differences between groups by the log rank test. Results There were 103 patients identified who underwent initial treatment with TACE for HCC. The median age was 60.5 (32.5-83.6) years. The median overall survival was 12.6 (0.23-55.95) months. The median survival in patients with a high (>5) pre-procedural NLR was 4.2 months compared to 15 months in those with a normal pre-procedural NLR (p=0.021). In those patients whose NLR either rose one month after treatment or did not remain normal, the survival was worse compared to those who normalized or remained normal (18.4 versus 9 months, p=0.006). The same was true at 6 months post-treatment (18.7 versus 9.5 months, p=0.002). An unresponsive NLR was associated with very poor outcome with median survival of 3.7 months (Figure). Multivariate analysis of age, gender, AFP, Milan inclusion, presence of extrahepatic disease (EHD), NLR and Child's score showed that Child's class B or C, presence of EHD and high NLR were independent factors associated with worse survival. Conclusion This study demonstrates that serum NLR measured before and after treatment is associated with outcome in patients with unresectable HCC undergoing TACE for initial therapy. Serum NLR is easy to calculate and is obtained from a routine complete blood count with differential, one of the more common blood tests measured in cancer patients. Along with liver function, serum NLR may be helpful to clinicians in providing prognostic information and determining best options for therapy or supportive care.



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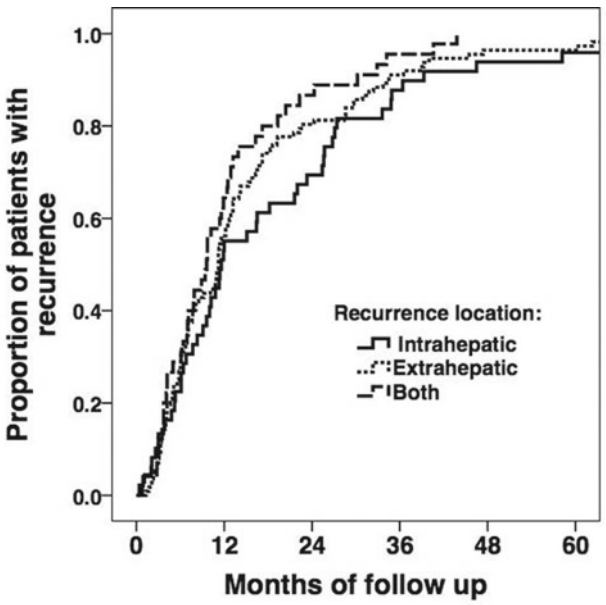
Patterns of Recurrence after Resection of Intrahepatic Cholangiocarcinoma: Results from 449 Patients I. Hatzaras,[1]* G. Sotiropoulos,[2] R. Schulick,[1] S. Alexandrescu,[3] C. Pulitano,[5] B. Clary,[6] A. Zhu,[7] A. Paul,[2] I. Popescu,[3] H. Marques,[4] E. Barroso,[4] L. Aldrighetti,[5] M. Choti,[1] R. Turley,[6] C. Ferrone,[7] T. Bauer,[8] D. Walters,[8] T. Gamblin,[9] K. Nguyen,[9] C. Hubert,[10] J. Gigot,[10] S. Meyer,[11] G. Mentha,[11] T.M. Pawlik.[1] *1. Surgery, John Hopkins University, Baltimore, MD; 2. University Hospital Essen, Essen, Germany; 3. Institute for Digestive Diseases and Liver Transplantation Fundeni, Bucharest, Romania; 4. Curry Cabral Hospital, Lisbon, Portugal; 5. Osped- ale San Raffaele, Milan, Italy; 6. Duke Medical Center, Durham, NC; 7. Massachusetts General Hospital, Boston, MA; 8. University of Virginia, Charlottesville,, VA; 9. University of Pittsburgh, Pittsburgh, PA; 10. Cliniques Universitaires Saint-Luc, Brussels, Belgium; 11. Hopitaux Universitaires de Geneve, Geneva, Switzerland.*

Introduction: Outcomes following surgical management of intrahepatic cholangiocarcinma (ICC) have largely focused on overall survival. Data on recurrence following surgery for ICC are limited. We sought to investigate rates and patterns of recurrence in patients following curative intent surgery for ICC. Methods: 449 patients who underwent surgery for ICC between 1973 and 2010 were identified from an international multi-institutional database. Clinicopathologic data, recurrence patterns, and recurrence-free survival (RFS) were analyzed. Results: Most patients had a solitary tumor (70%) with a median tumor size of 6.5 cm. The majority of lesions did not have vascular invasion (69%). Surgical treatment was < hemi-hepatectomy (47%), hemi-hepatectomy (26%), or extended hepatectomy (27%). On pathology, 23% patients had lymph node metastasis and 18% had a microscopically positive (R1) margin. A subset of patients received adjuvant chemotherapy (32%) or chemoradiation (39%). While 5-year overall survival was 31%, 351 (78%) patients recurred with a median RFS time of 13.2 months. First recurrence site was intra-hepatic only (54%), extra-hepatic only (24%), intra- and extra-hepatic (22%). There was no difference in RFS based on site of recurrence (intra-hepatic: 11.2 months; extra-hepatic 11.6 months; intra- and extra-hepatic: 9.6 months; P=0.16). An R1 surgical margin (HR: 1.56, p=0.02) and neural invasion (HR: 1.55, p=0.02) were associated with overall recurrence, while male gender (HR: 1.70, p=0.011), >50% liver parenchyma resection (HR: 1.97, p=0.03), primary tumor size (1.05, p=0.02), and poor differentiation (HR: 1.92, p=0.01) were associated with intrahepatic recurrence. Receipt of adjuvant therapy was not associated with risk of recurrence (P>0.05). Conclusion: Over 75% of patients developed recurrence following curative intent surgery for ICC. The pattern of failure was distributed relatively equally with half of patients recurring with liver only disease while half had an extrahepatic metastatic site of recurrence. Future efforts

need to be directed toward identifying more effective adjuvant regimens given the high rate of recurrence.



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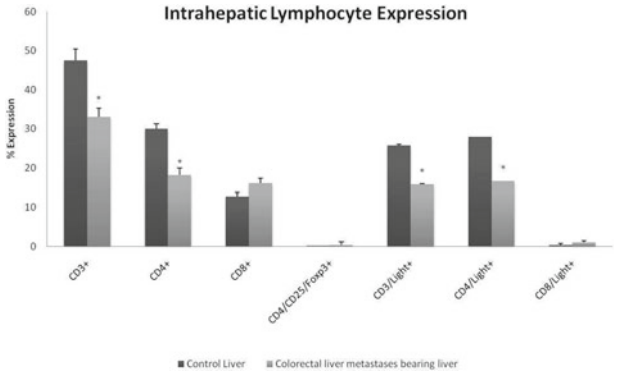
Intrahepatic Lymphocytes have Decreased LIGHT Expression in a Model of Isolated Colorectal Liver Metastases A.V. Maker,[1]* J.Z. Qin,[2] B.S. Prabhakar.[2] *1. University of Illlinois at Chicago, Department of Surgery, Division of Surgical Oncology; Department of Mictobiology and Immunology, Chicago, IL; 2. University of Illlinois at Chicago, Department of Microbiology and Immunology, Chicago, IL.*

<p> **Introduction:** Our preliminary studies identified T-cell proliferation as the most significant biologic process associated with survival in patients with colorectal liver metastases (CRLM). The protein LIGHT (TNFSF14) stimulates effector T-cell proliferation and has been shown to induce an anti-tumor response in established tumors. Further characterization of LIGHT in the immune milieu of CRLM is needed.<p> **Methods:** A model of isolated CRLM mimicking the human course was established in immunocompetent Balb/C mice. Metastatic disease was confirmed by in-vivo bioluminescent imaging and at autopsy. Tumor infiltrating lymphocytes (TIL) and peripheral blood mononuclear cells (PBMC) were isolated and evaluated for phenotypic and functional properties utilizing flow cytometry. LIGHT transcript expression was evaluated by polymerase chain reaction.<p> **Results:** Populations of CD3+ and CD4+ T-cells were decreased in tumor bearing livers compared to control (p=0.02, 0.005). There was no difference in the total number of CD8 or regulatory T-cell (CD4CD25Foxp3+) populations between the groups, though CD4+ and CD8+ cells were significantly activated in tumor bearing livers as determined by CD69 and CD107a expression. Expression of LIGHT was decreased in CD3+ (26 ± 2% vs. 16% ± 4%, p=0.02) and CD4+ (28 ± 2% vs. 17 ± 4%, p=0.01) intrahepatic T-cells from tumor bearing livers, and was expressed at very low levels in CD8+ intrahepatic T-cells. Similarly, LIGHT expression was decreased in both CD3+ (41% vs. 31%) and CD4+ (41 vs. 32%) T-cells and minimally expressed in CD8+ T-cells (<1%) from PBMC in tumor bearing mice compared to controls. Conversely, protein transcript expression of LIGHT and its receptor HVEM were increased in tumor bearing liver compared to normal liver. <p> **Conclusion:** LIGHT expression is decreased in intrahepatic lymphocytes and PBMC from tumor bearing animals. Methods to increase LIGHT expression in TIL and in the tumor microenvironment may be a promising immunotherapeutic strategy and warrants further research.



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Predicting Outcome after Hepatectomy for Metastatic Colorectal Cancer: Is the Answer in the Primary Tumor? K. Cardona,* F. D'Amico, J. Shia, M. Gönen, M.R. Weiser, P.B. Paty, T.P. Kingham, P.J. Allen, R.P. DeMatteo, Y. Fong, W.R. Jarnagin, M.I. D'Angelica. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Outcome after hepatic resection for colorectal liver metastases (CRLM) is heterogeneous and accurate predictors of survival are lacking. The aim of our study was to analyze the prognostic relevance of pathologic details of the colorectal primary tumor in patients undergoing hepatic resection of CRLM. Methods: Retrospective review of a prospective database identified patients who underwent potentially curative hepatic resection of CRLM. Clinicopathological variables were investigated and their association with outcome was analyzed. Results: From 1997-2007, 1004 patients underwent hepatic resection for CRLM. The median follow-up for survivors was 59 months with a 5-year predicted survival of 47%. Ninety-two percent of patients received perioperative chemotherapy and 34% received adjuvant hepatic artery infusion chemotherapy. Univariate analysis identified 10 factors associated with poor survival. Three of these related to the pathology of the primary tumor: lymphovascular invasion (LVI, p<0.0001), perineural invasion (p=0.005), and degree of regional lymph node involvement (N0 vs N1 vs N2, p<0.0001). Multivariate analysis identified 7 factors associated with poor survival. Two of these related to the pathology of the primary tumor: LVI (HR 1.3, 95% CI 1.06-1.64, p=0.01) and degree of regional lymph node involvement where an increase in the number of metastatic regional lymph nodes from N1 (HR 1.3, 95% CI 1.04-1.69, p=0.02) to N2 (HR 1.7, 95% CI 1.27-2.21, p <0.0005) was associated with a reduced survival. LVI positive patients had a median survival of 48 months compared to 69 months for LVI negative patients (p<0.0001); moreover, patients who were LVI positive with N2 nodal disease had a reduced survival to 40 months compared to 74 months for patients who were LVI negative with no nodal disease (p<0.0001). Conclusion: Resection of CLRM is associated with long-term survival. Pathologic details of the primary colorectal tumor, particularly LVI and the degree of lymph node involvement, are strong predictors of survival. Future biomarker studies should consider utilizing factors related to the primary colorectal tumor.

Survival related to LVI and degree of regional lymph node involvement

Pathologic variable	Median Overall Survival*	5-yr Survival
LVI negative/N0 (n=242)	74 months	60%
LVI negative/N1 (n=140)	58 months	49 %
LVI positive/N0 (n=69)	54 months	44%
LVI positive/N1 (n=131)	53 months	43%
LVI positive/N2 (n=131)	40 months	30%

*p <0.0001 (Log-rank test); LVI: lymphovascular invasion; N0: no metastatic regional lymph nodes; N2: ≥4 positive metastatic regional lymph nodes

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Efficacy of Adjuvant Therapy after Resection of Colorectal Liver Metastases: The Predictive Value of the MSKCC Clinical Risk Score
J. Weitz,* N.N. Rahbari, C. Reissfelder, M. Koch, M.W. Büchler.
Department of Surgery, University of Heidelberg, Heidelberg, Germany.

Introduction It has remained uncertain, if patients with colorectal cancer liver metastases (CLM) should receive adjuvant therapy. The available randomized controlled trials lacked sufficient power and failed to provide a clear advantage favoring adjuvant chemotherapy. As these studies did not stratify their study cohorts regarding the risk of poor outcome, clinical or molecular predictors may help to select those patients at high risk for disease recurrence who obtain a survival advantage by adjuvant chemotherapy. It was the aim of the present study to identify high-risk subgroups of patients with CLM who benefit from adjuvant therapy after potentially curative resection. Methods A total of 316 patients with potentially curative resection of CRC liver metastases were enrolled from a prospective database. Inclusion criteria were no neoadjuvant therapy, no extrahepatic disease and negative resection margins. The primary endpoint was overall survival. Patients' risk status was evaluated using the Memorial Sloan-Kettering Cancer Center clinical risk score (MSKCC-CRS). Multivariable analyses were performed using Cox proportional hazard models. Results: A total of 137 (43%) patients had a MSKCC-CRS > 2. Adjuvant chemotherapy was administered to 116 (37%) patients. Patients who received adjuvant chemotherapy were of younger age ($p = 0.03$) with no significant difference in the presence of multiple metastases ($p = 0.72$) or bilobar metastases ($p = 0.08$). On multivariate analysis adjuvant chemotherapy was associated with improved survival in the entire study cohort (Hazard ratio 0.69; 95% confidence interval 0.69 – 0.98). In high-risk patients with a MSKCC-CRS > 2 adjuvant chemotherapy was associated with a marked survival advantage (HR 0.40; 95% CI 0.23 – 0.69), whereas it was of no benefit in patients with a MSKCC-CRS ≤ 2 (HR 0.90; 95% CI 0.57 – 1.43). Conclusions The MSKCC-CRS offers a tool to select patients for adjuvant therapy after resection of CLM. It should be used to stratify patients in future studies on adjuvant therapy after resection of CLM.

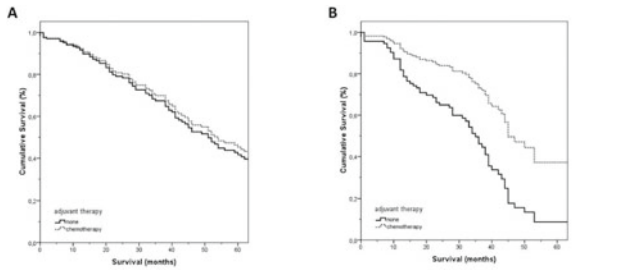

Figure 1

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The Role of Neoadjuvant Chemotherapy in Patients with Resectable Colorectal Liver Metastases N. Ayez,[1]* D.J. Grunhagen,[1] J. De Jonge,[1] J.N. Ijzermans,[2] A.M. Eggermont,[3] C. Verhoef.[1] *1. Surgical oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 2. Erasmus University MC, Rotterdam, Netherlands; 3. 3 Institut de Cancérologie Gustav Roussy, Villejuif, France.*

Introduction: The combination of hepatic resection and chemotherapy is increasingly accepted as an effective treatment for patients with colorectal liver metastases (CRLM). However, controversy remains regarding the surgery-chemotherapy (CTx) sequence and if all patients with CRLM benefit from peri-operative CTx in terms of survival. In 1999, Fong et al. described the most widely used clinical risk score (CRS) today. We investigated the survival benefit of neoadjuvant CTx in resectable CRLM, stratified by the Fong CRS. Methods: Between January 2000 and December 2009 all patients who underwent liver resection for CRLM were analyzed. All patients with extrahepatic disease and missing values needed to calculate the CRS of Fong were excluded. We compared survival rates of patients with and without neoadjuvant CTx stratified by the CRS. None of the patients received adjuvant CTx after liver surgery. Fong's score includes five risk factors and defines two risk groups; Low CRS 0-2 risk factors and High CRS 3-5 risk factors. Results: The median age was 63 years (30-86) and the majority of the patients was male (64%). Prior to liver resection for CRLM, 220 patients had a low CRS of which 65 received neoadjuvant CTx. A total of 144 patients had a high CRS of which 88 received neoadjuvant CTx. The median follow up was 35 months (0-131). In patients with a low CRS, there was no significant difference in median overall survival (OS) between patients with and without CTx, 54 months (41-66) and 65 month (39-91) respectively, $p=0.589$. In patients with a high CRS, there was a significant difference in median OS between patients with and without CTx, 67 months (38-96) and 33 month (29-37) respectively, $p=0.003$. Conclusion: In our single center series of patients with CRLM, patients with a high CRS might benefit from neoadjuvant CTx. In patients with a low CRS neoadjuvant CTx seems not beneficial.

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BRAFV600E Mutation Independently Predicts Central Compartment Lymph Node Metastasis in Patients with Papillary Thyroid Cancer G. Howell,* M.N. Nikiforova, S.E. Carty, M.T. Stang, K.L. McCoy, M.J. Armstrong, S.P. Hodak, Y.E. Nikiforov, L. Yip. *University of Pittsburgh, Pittsburgh, PA.*

Introduction: The role of central compartment neck dissection (CND) in the management of papillary thyroid cancer (PTC) remains incompletely defined and the preoperative identification of patients at elevated risk for central compartment lymph node metastasis (CLNM) is imperfect. The aim of this investigation was to examine if available preoperative clinical parameters, including BRAFV600E mutation status which may predict poor prognosis, can also predict CLNM. Methods: In 2009, CND was systematically implemented into our management algorithm for patients with a preoperative diagnosis of PTC, BRAF detected on fine needle aspiration biopsy, and/or suspicion of CLNM by ultrasound or intraoperative evaluation. When unknown preoperatively, BRAF status was routinely obtained for PTC diagnosed histologically. Under an IRB-approved protocol, we conducted a single center, retrospective review of all patients who had initial thyroidectomy for histologic PTC during 2010. The presence of CLNM was examined for correlation to preoperative clinical parameters including tumor size, gender, age and BRAF mutation status. Results: CND was performed in 157/224 (70%) patients with histologic PTC and there was no difference in the proportion who were BRAF positive versus BRAF negative (54% v. 46%, p=.14). The mean number of lymph nodes evaluated was 5 (sd ±4), and CLNM was diagnosed in 38% (59/157). On univariate analysis, only BRAF positivity was associated with CLNM (BRAF, p=.001; tumor size >2 cm, p=0.29; male gender, p=0.15; age >45 years, p=.44). On multivariate analysis, BRAF positivity remained an independent predictor of CLNM (RR 3.3, p=.001). By AJCC criteria, the presence of CLNM served to upstage 6/125 (5%) patients who were >45 years old and in 4/6 such patients, CND was performed because of BRAF positivity. Conclusion: The presence of BRAFV600E is an independent predictor of CLNM. Our findings support the routine use of preoperative molecular testing results to guide the extent of initial surgery. To optimize pathologic staging of papillary thyroid cancer, CND should be considered for all patients who are BRAF positive.

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Simultaneous Medullary and Differentiated Thyroid Cancer: A Population-level Analysis of an Increasingly Common Entity
R. Wong,* H.S. Kazaure, S.A. Roman, J.A. Sosa. *Yale University School of Medicine, New Haven, CT.*

INTRODUCTION: Simultaneous medullary thyroid carcinoma (MTC) and differentiated thyroid carcinoma (DTC) are rare. This study provides the first population-level analysis of the characteristics and outcomes of patients with simultaneous MTC and DTC. METHODS: Using SEER (1988-2008), patients with simultaneous MTC/DTC were retrospectively compared to those with MTC alone. Data were analyzed using $\chi 2$, ANOVA, and log-rank tests. RESULTS: There were 162 patients with simultaneous MTC/DTC and 1,699 with MTC alone. Of patients with simultaneous MTC/DTC, MTC was diagnosed first in 67.9% of cases. As a percentage of all patients with MTC, simultaneous MTC/DTC increased from 0.6% in 1988-97 to 2.0% in 1998-2002 and 6.0% in 2003-08. Compared to MTC alone, simultaneous MTC/DTC was associated overall with smaller MTC tumor size (mean 2.9 cm vs 2.2 cm; p=.005) as well as lower rates of MTC extrathyroidal extension (25.4% vs 16.8%;

p=.015) and distant metastases (15.7% vs 9.3%; p=.032). DTC mean tumor size was 0.9 cm, with 10.3% showing extrathyroidal extension, and 1.5% showing distant metastases. When patients came to medical attention for DTC rather than MTC, their mean MTC tumor size was smaller (p=.01); this was not the case in those patients who were diagnosed with MTC first, as their tumor sizes were similar to those diagnosed with MTC alone. There was no difference between MTC alone and simultaneous MTC/DTC in number of lymph nodes examined or number of nodes positive for MTC. Compared to MTC alone, patients with simultaneous MTC/DTC were more likely to receive thyroidectomy (84.7% vs 93.2%; p=.003) and radioisotopes (4.4% vs 25.0%; p<.001). The overall mortality rates for simultaneous MTC/DTC vs. MTC alone were 13.6% and 23.7%, respectively (p=.003). Cause-specific mortality for simultaneous MTC/DTC was less compared to that of MTC alone (10-year survival rates 87% vs 81%, p=.056). CONCLUSIONS: Patients with simultaneous MTC/DTC appear to be diagnosed earlier in tumor development than those with MTC alone and have a better prognosis. This entity likely represents a primary tumor with an incidental pathologic finding of a second malignancy.

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The Value of Intraoperative Parathyroid Hormone Monitoring (IOPTH) and Multi-modal Localization in Reoperative Parathyroid Surgery (REOPS) J. Avise, C.J. Weber, J. Sharma.* *Surgery, Emory University School of Medicine, Atlanta, GA.*

Introduction The aim of this study was to evaluate cure rates, pathology, complications, and efficacy of adjuncts such as IOPTH, preoperative sestamibi, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US) and intraoperative venous sampling/localization (IVSL) for REOPS in primary sporadic hyperparathyroidism (PHPT). Materials and Methods Between 1992-2010, 1689 consecutive patients underwent parathyroidectomy (PTX). Of these, 324 REOPS were performed in 214 referral patients with persistent/recurrent PHPT and 89 patients who had had a previous neck surgery without a PTX. IOPTH was used in 231 operations, sestamibi=324, CT=192, MRI=72, US=98, and IVSL=34. Results IOPTH was the single most useful adjunct and improved the cure rate from 76.1% to 93.8% (p<0.01) with a mean follow-up of 2.6 ± 0.6 years. When IOPTH dropped to normal (n= 203), after excision of the parathyroid tumors, cure rate was 99.4%. However, when IOPTH did not normalize (n=28), cure rate was only 60.7%. When preoperative imaging localized a lesion, a tumor was identified in that location in 74.1% of sestamibi scans, 67.7% of CT, 60.9% of MRI and 44.8% of US. IVSL accurately lateralized 78.6% of tumors. When at least 2 imaging modalities were concordant, sensitivity improved to 91.6% (p<0.001). In patients with persistent PHPT, 32% had single adenomas, 64% had multiple gland disease, 3% had parathyroid cancer and 1% had another malignancy. Nephrolithiasis occurred more commonly in REOPS than denovo PTX, 41% vs. 22% (p=0.02). Rates for temporary hypocalcemia, permanent hypocalcemia and recurrent nerve palsy were 17.3%, 0.67% and 0.3%, respectively. Post-operative hospital stay was longer in REOPS than denovo PTX, 1.9 ± 0.9 vs. 1.1 ± 0.7 days, respectively (p<0.0001). Conclusions This is the largest series evaluating outcomes in REOPS for PHPT. IOPTH improves outcomes in REOPS. No single localization modality is ideal and multiple imaging modalities are optimal for success. REOPS have an increase length of stay possibly related to an increased need for intravenous calcium supplementation.

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The Value of Preoperative Imaging in Ileal Neuroendocrine Tumors F.S. Dahdaleh,* A.W. Lorenzen, J.C. Carr, J. Liao, T.M. O'Dorisio, J.R. Howe. *Surgery, Univ of Iowa, Iowa City, IA.*

Introduction: Neuroendocrine tumors (NETs) of the ileum are a rare but important subgroup of malignancies whose incidence has been increasing. Since 30% of ileal NETs present with metastatic disease, often with an occult primary site, preoperative imaging is critical for determining who will benefit most from abdominal exploration. We set out to evaluate the usefulness of the two most commonly performed imaging modalities in predicting the extent of disease found at exploration in patients with ileal NETs. Methods: A retrospective chart review was performed on patients with ileal NETs resected at one institution. Data from preoperative computed tomography (CT) scans were reviewed to determine whether the primary tumor, nodal, or liver metastases were seen, then compared to intraoperative findings. Results of preoperative Octreoscans were similarly examined, except that primaries and nodes were combined as one category due to the lower resolution of these scans. Results: Between 1998 and 2011, we operated upon 62 patients with ileal NETs. Of these patients, 47/62 (77%) had distant metastases and 47/57 (82%) had nodal metastases at exploration. Fifty-nine patients had preoperative CT scans and 50 had Octreoscans. Using CT, a primary tumor was visualized and localized to the ileum in 36/59 (61%) of cases (described as a mass or small bowel thickening). The imaging findings are summarized in the Table. There were no cases in which primaries/nodes were identified by Octreoscan but not by CT. Conclusions: Preoperative abdominal imaging is helpful in localization and decision making in patients with ileal NETs. Although frequently useful for identifying occult extrahepatic sites of metastatic disease, we found that Octreoscans provided limited additional information relative to CT in identifying ileal NETs or their corresponding nodes. The majority of CT scans suggested the presence of a primary ileal tumor or enlarged regional nodes, which facilitated the decision to operate. However, since 20% of ileal NETs were not identified by imaging preoperatively, surgical exploration still plays an important role in patients with negative imaging and clinical suspicion of ileal NET.

	CT Scan	Octreoscan
Primary Visualized	36/59 (61%)	
Mass	27/36 (75%)	--
Thickening	9/36 (25%)	
Nodes Visualized	31/59 (53%)	--
Any Intraabdominal (Primary or Nodes)	47/59 (80%)	37/50 (74%)
Distant Metastasis	40/47 (85%)	34/41 (83%)
Single focus	4/40 (10%)	--
Multiple	36/40 (90%)	--

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Ultrasound Should Not Guide the Timing of Thyroidectomy in Pediatric Patients Diagnosed with MEN2A through Genetic Screening L.F. Morris,* B.S. Edeiken, J.E. Lee, S.G. Waguespack, A.K. Ying, C.L. Warneke, N.D. Perrier, E.G. Grubbs. *University of Texas MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: American Thyroid Association (ATA) recommendations for delay of thyroidectomy in pediatric MEN2A patients (pts) include consideration of normal serum calcitonin (Ct) and normal neck ultrasound (US). We hypothesized that a normal neck US would not exclude a medullary thyroid cancer(MTC) diagnosis on final pathology. METHODS: We retrospectively queried a MEN2A database for pediatric pts(age < 18), diagnosed through genetic screening, who underwent preoperative (preop) US and thyroidectomy at our institution. Using ATA definitions, an abnormal US was defined as any concerning thyroid lesions ≥5 mm. Preop US and Ct results were compared with final pathologic findings of MTC. RESULTS: The 36 pts included in this study ranged in age from 1.8 to 14.3 years old (median 6.3 years). 16 pts (44%) had MTC on final pathology. Pts with MTC had a median age of 8.10 (range 3.75 – 14.29) and those without MTC had a median age of 5.76 years (range 1.83 to 12.44 years)(p=.08) The average size of MTC on pathologic specimens was 3.0 mm (range 0.5-7 mm SD 1.7). 3/16 pts who had MTC had an abnormal US. The sensitivity of an abnormal US in predicting MTC was 19% (95% CI 0.04, 0.46) and the specificity was 95% (95% CI 0.75, 1.00). Elevated Ct detected MTC in 14/16 pts [sensitivity of 88% (95% CI 0.62, 0.98), specificity of 35% (95% CI0.15, 0.59)]. The area under the ROC curve (AUC) for using US lesion size to predict MTC was 0.52 (95% CI 0.36,0.69), suggesting a poor discriminating ability between MTC and non-MTC cases. The AUC for Ct level (fold increase above normal) was improved at 0.67 (95% CI 0.49, 0.86), however was no better at discriminating MTC than was age (AUC 0.67, 95% CI 0.48,0.86). CONCLUSIONS: In the pediatric population diagnosed with MEN2A by genetic screening, preop US of the thyroid was not sensitive in detecting MTC tumors of any size. This modality should be used with caution when making decisions to delay thyroidectomy in this group. In this setting, in which early cancer detection is of greatest importance, more emphasis should be placed on Ct status.

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Chrysin Activates Notch1 Signaling and Suppresses Tumor Growth of Anaplastic Thyroid Carcinoma In Vitro and In Vivo X. Yu,* T. Phan, P.N. Patel, R. Jaskula-Sztul, M. Kunnimalaiyaan, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

Background: The extremely poor prognosis of anaplastic thyroid carcinoma (ATC) reflects the lack of curative therapy for this very aggressive malignancy. Recently, the Notch1 signaling pathway, which affects cell proliferation and differentiation, has been found to be aberrantly inactivated in ATC. However, it is unknown whether activation of Notch1 is able to inhibit ATC cellular growth. In this study, we evaluated whether Chrysin, a Notch1 inducer reported in other malignancies, can activate Notch1 signaling and suppress tumor growth of ATC both in vitro and in vivo. Method: Human ATC cell lines, HTh7 and KAT18, were treated with 25 and 50μM (around IC50) of Chrysin, and the activation of Notch1 pathway was then assessed by both real-time PCR and CBF binding assay. To further evaluate the drug effects in vivo, nude mice s.c. injected with ATC cells were either treated with Chrysin (75mg/kg) or vehicle by oral administration every day for 21 days. Tumor size was measured every other day and the xenografts were collected for molecular analysis. Results: The Notch1 mRNA expression level was elevated with Chrysin treatment, and so did Hes1, a Notch1 down-stream effector, suggesting Chrysin triggers the signaling cascade. A dose-dependent increase in Notch1 activity, as evidenced by the luciferase enhancement, was also observed using CBF1 binding assay. Chrysin treatment in nude mice suppressed the growth of ATC xenografts by an average of 59% (tumor volume) compared with the control group (p=0.002). In addition, calculated median time to tumor progression was 11 days for control mice while reached 21 days for Chrysin treatment group (p=0.008). Analysis of Chrysin-treated ATC tumors revealed an increase in the active intracellular domain of Notch1 protein. Besides, activation of Notch1 in vivo was associated with the induction of cleaved poly ADP-ribose polymerase protein, indicating that the growth inhibition was due to apoptosis. Conclusion: The novel Notch1 activator Chrysin inhibits tumor growth in ATC both in vitro and in vivo. Therefore, Chrysin could be a promising therapeutic candidate for ATC, which justifies further clinical studies.

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Effects of Prophylactic Central Compartment Neck Dissection on Serum Thyroglobulin and Recommendations for Radioactive Iodine Adjuvant Therapy in Patients with Differentiated Thyroid Cancer T.S. Wang,* D.B. Evans, T.W. Yen. *Medical College of Wisconsin, Milwaukee, WI.*

Background: Controversy exists in the management of patients with differentiated thyroid cancer (DTC). The purpose of this study is to examine the effect of prophylactic central compartment neck dissection (CCND) on thyroglobulin (Tg) levels and recommendations for radioactive iodine adjuvant therapy (RAI) at a single high-volume center. Methods: The records of 107 patients undergoing surgery for DTC between 1/09-11/10 were reviewed. Prophylactic CCND is defined as removal of central compartment lymph nodes with no preoperative evidence of lymphadenopathy. Institutional protocol for RAI includes recombinant thyrotropin (rhTSH) for patients at low risk for recurrence, thyroid hormone withdrawal (THW) for medium/high risk patients, and pretreatment scan. Patients with undetectable Tg levels and no uptake do not undergo RAI. Results: All patients had a total thyroidectomy. Therapeutic CCND was performed in 17 (16%) patients and prophylactic CCND in 49 (46%). Of the 49, 20 (41%) patients had metastatic disease (median 2 lymph nodes, range 1-12). Overall, detection of metastatic disease changed AJCC staging in 13 patients ≥45 years and recommendations for RAI in 17 patients: 11 underwent THW after being upgraded to medium-high recurrence risk and 6 received RAI who otherwise would not have. In addition, 2 patients who underwent prophylactic CCND had negative pretreatment scans and did not receive RAI. There was no difference in Tg at the time of RAI between any of the groups (p=0.38). Excluding patients with known distant metastatic disease, no patient in any group has evidence of recurrent DTC on imaging or by serum Tg (median 0.5, range 0.2-1.9) at follow-up (median, 11 months). Conclusion: Prophylactic CCND resulted in detection of metastatic lymphadenopathy in 20 (41%) patients and changed RAI recommendations in 19 (38%). To date, there is no difference in serum Tg levels in patients undergoing therapeutic, prophylactic, or no CCND, either at time of RAI or after. Longer follow-up is needed to detect potential differences in recurrent disease or long-term effects of RAI

CCND	Nodal status	n	Median tumor size (cm)	Recurrence risk (n,%)		RAI recommended (n,%)	Median Tg at RAI (range)	Median dose, 131-I (range)
				Low*	Medium/High§			
None	Nx	41	0.6	36 (88)	5 (12)	12 (36)	2.2 (0.5-18,131)	105 (52-107)
Prophylactic	N0	29	1.5	24 (83)	5 (17)	15 (52)	0.7 (0.2-1,359)	103 (76-152)
	N1	20	1.4	6 (30)	14 (70)	20 (100)	1.3 (0.5-40.2)	105 (77-156)
Therapeutic	N1	17	2.0	2 (12)	15 (88)	17 (100)	3.1 (0.5-66.5)	102 (77-159)

* Low risk: Age <45: T1-2N0,T1-3N1a, Age ≧45: T1b-2N0; § High risk: Age <45: Any T4, Any TN1b, Age ≧45: Any T3-4, Any TN1a-b

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Robotic Versus Laparoscopic Resection of Large Adrenal Tumors O. Agcaoglu, S. Aliyev, J. Mitchell, A. Siperstein, E. Berber.* *Cleveland Clinic, Cleveland, OH.*

Background: Although, recent studies have shown the feasibility and safety of robotic adrenalectomy, an advantage over the laparoscopic approach has not been demonstrated. Our hypothesis was that the use of the robot would facilitate minimally invasive resection of large adrenal tumors. Methods: Between 2000 and 2011, 227 adrenalectomies were done at a single institution. Adrenal tumors ≥ 5 cm resected robotically were compared to those removed laparoscopically from a prospective IRB-approved database. Clinical and perioperative parameters were analyzed using Student t and Chi-square tests. All data are expressed as mean ± SEM. Results: There were 25 patients in the robotic and 38 in the laparoscopic group. While the groups were similar regarding age and gender, body mass index was smaller in the robotic (27.1 ± 0.8) compared to the laparoscopic patients (30.2 ± 0.9), p=0.029. Tumor size was similar in both groups (6.5 ± 0.4, range: 5-12 cm, versus 6.2 ± 0.3, range: 5-15 cm, respectively, p=0.661). Operative time was shorter for the robotic versus laparoscopic group (159.4 ± 13.4 vs 187.2 ± 8.3 minutes, respectively, p=0.043); while, estimated blood loss was similar (83.6 ± 59.4 vs 166.6 ± 51.2, respectively, p=0.147). The conversion to open rate was less in the robotic (4%) versus the laparoscopic (11%) group, p=0.043. Hospital stay was shorter for the robotic group (1.4 ± 0.2 versus 1.9 ± 0.1 days, respectively, p=0.009). The 30-day morbidity was zero in the robotic and 5% in the laparoscopic group. Pathology was similar between groups, with 1 adrenocortical carcinoma identified in each group. Conclusions: Our study shows that the use of the robot shortens operative time and decreases the rate of conversion to open for adrenal tumors larger than 5 cm. Robotic adrenalectomy has become our preferred surgical approach for removing large adrenal tumors.

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Single Dose Prophylactic Octreotide Does Not Prevent Intraoperative Carcinoid Crisis K. Massimino,* O. Harrskog, S. Pommier, R. Pommier. *Surgery, Oregon Health & Science University, Portland, OR.*

Introduction: Surgery and anesthesia in carcinoid patients can provoke a carcinoid crisis, which can have serious sequelae, including death. Octreotide prophylaxis is recommended to prevent carcinoid crisis, however there are few reports of outcomes and no large series examining its efficacy. We hypothesized that prophylactic octreotide alone is not sufficient to prevent carcinoid crisis. Methods: Records of carcinoid patients undergoing abdominal operations during years 2007-2011 were retrospectively reviewed. Effect of clinical factors including octreotide use on intraoperative hemodynamic events (systolic blood pressure < 80 for > 10 minutes or report of hemodynamic instability including hypotension, hypertension, tachycardia or carcinoid crisis) was determined. Association of intraoperative hemodynamic events with postoperative outcomes was evaluated. Rates of intraoperative events in patients treated with octreotide prophylaxis were compared to historic controls. Results: Ninety-seven intraabdominal operations performed by a single surgeon were reviewed. Ninety percent of patients received preoperative prophylactic octreotide. Fifty six percent received at least one additional intraoperative dose. Twenty three patients (24%) all of whom received prophylactic octreotide experienced a major intraoperative hemodynamic event. This rate is higher than previously published. Intraoperative hemodynamic events correlated with presence of hepatic metastases but not presence of carcinoid syndrome. Post operative complications occurred in 60% of patients with intraoperative hemodynamic events versus 31% of those with none (p=0.01). Conclusions: Significant intraoperative hemodynamic events occur frequently in carcinoid patients with hepatic

metastases regardless of presence of carcinoid syndrome and despite single dose prophylactic octreotide. Occurrence of such events correlates strongly with post-operative complications. Randomized controlled trials are needed to determine whether the administration of prophylactic octreotide is beneficial.

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Incidence of Incidentally Identified Micropapillary Cancer (MPC) in Patients Undergoing Thyroidectomy K.K. Shah,[1]* P. Shah,[1] C. Hopkins,[2] G. Karakousis,[1] R. Kelz,[1] D. Fraker.[1] *1. Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA; 2. Harrison Department of Surgical Research, Philadelphia, PA.*

Introduction: Micropapillary cancer (MPC) is a common finding in patients undergoing surgery for thyroid disease. While the natural history of MPC is not well characterized, its incidence in patients undergoing thyroidectomy with varying pre-operative clinical suspicion is understudied. Methods: We performed a retrospective cohort study of 3196 patients undergoing surgery by a single surgeon between January 1997 and June 2011. MPC was defined as the presence of papillary cancer with size < 1 cm on final pathology. Preoperative patient characteristics, FNA findings, intraoperative findings and the final pathology were reviewed for these patients and descriptive statistics were performed. Results: Among 2954 patients who underwent thyroidectomy without prior thyroid surgery, MPC was identified in 802 patients (27%). 94% of patients underwent preoperative FNA. Median age of these patients was 51 years and 76% were females. Excluding patients with papillary thyroid cancer (PTC) on final pathology (n=1122), the incidence of MPC was 25%. MPC incidence in patients undergoing surgery for benign disease (with either no pre-operative FNA or benign FNA results) was 23% (119/516 patients). The incidence of MPC in patients with either follicular lesion of uncertain significance (FLUS) or follicular neoplasm results was 34% (392/1155 patients). These were similar with respect to age (median age of 50 years in the benign group v/s 50.5 in the other group). Results: MPC is incidentally discovered in approximately one-quarter of patients undergoing thyroidectomy. The incidence appears higher in those patients with FNA with follicular features as compared to those operated on with a benign pre-operative diagnosis.

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Association of Type-O Blood with Pancreatic Neuroendocrine Tumors in Von Hippel-Lindau Syndrome A. Weisbrod,* D. Liewehr, S. Steinberg, E. Patterson, M. Linehan, N. Nilubol, E. Kebebew. *Endocrine Oncology Section, Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.*

Background: ABO blood type antigens are expressed not only on human red blood cells, but throughout the gastrointestinal tract and normal pancreatic tissue. There have been conflicting reports regarding the association between ABO blood type and various malignancies. In this study, we analyzed the association of ABO blood type and the manifestation of pancreatic disease in a high-risk cohort of patients with Von Hippel-Lindau (VHL) syndrome. Methods: A retrospective review of 798 patients with VHL syndrome was performed. Fisher's exact test and Mehta's modification to Fisher's exact test were used to identify if an association was present between ABO blood type and manifestations of VHL syndrome. Results: There was no significant difference in age, gender, germ line VHL exon mutation, and blood type in the study cohort. The frequency of blood types in the study cohort were similar to the United States population distribution. We found statistically significant associations between O blood type and pancreatic manifestation of VHL syndrome (p=0.0475). Further stratifications of pancreatic disease showed significant associations of non-O blood type with cystic disease (p=0.0460) as well as O blood type with solid pancreatic disease (p=0.0084). Moreover, patients with pancreatic neuroendocrine tumors who required surgical intervention based on tumor growth and size tended to have blood type O (p=0.0506). Conclusions: Our findings suggest a higher risk of pancreatic neuroendocrine tumors in VHL syndrome in patients with an O blood type. This information could be useful for guiding surveillance decisions to detect and/or monitor pancreatic manifestations of patients with VHL.

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Detecting Hereditary Nonpolyposis Colorectal Cancer Syndrome (HNPCC) in Colorectal Cancer (CRC) Patients: Optimal Strategies at Lower Costs D.E. Abbott,* S.B. Cantor, M.A. Rodriguez-Bigas, G.J. Chang, P.M. Lynch, B.W. Feig, J.M. Skibber, N. You. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Background The optimal strategy to detect HNPCC in CRC patients remains controversial, and may include testing tumors for microsatellite (MSI) status and/or patients for mutations in DNA mismatch repair (MMR) genes. The costs of 6 testing strategies were compared against their risks of missing patients who need to be managed as HNPCC. Methods 185 consecutive CRCs were prospectively tested by both immunohistochemistry (IHC, for protein expressions of MLH1, MSH2, MSH6, PMS2) and PCR-based MSI. Secondary tests included MLH1 promoter methylation, BRAF mutation, and germline mutation, as appropriate. Patients managed as HNPCC included those with pathogenic germline mutations, and also those with a germline variant of unknown significance or uninformative negative result in the setting of non-sporadic MSI-high CRC (unmethylated MLH1 promoter, or BRAF and TACSTD wild-type). A decision tree compared the strategy of performing both IHC and MSI in all (Strategy 1) to five alternatives (Strategies 2-6, Table). Costs were obtained from commercial list prices, Medicare reimbursement, and literature; probabilities were calculated from patient data. Incremental cost-effectiveness ratios (ICERs) were reported for each additional patient identified to be managed as HNPCC. Results Twenty (10.8%) patients were identified as being managed as HNPCC. Performing IHC and MSI in all (Strategy 1) or IHC first in all followed by MSI when IHC was normal (Strategy 4) detected all 20 cases. When compared to performing IHC only (Strategy 2), Strategy 4 demonstrated an ICER of $31,821 per additional case detected, while other strategies were more costly and/or less effective (Table). Between the two strategies that detected all cases of HNPCC, Strategy 4 was less costly ($1,049 vs $1,098 per patient, Table). Conclusions There is increasing interest in universal testing of all CRC patients for HNPCC. When combined with appropriate secondary and confirmatory testing, performing IHC and MSI in all or IHC in all followed by MSI when IHC were normal, both showed a zero miss rate, while the latter was slightly more cost-effective.

Strategy	Description	Detect rate (%)	Cases missed (number)	Cost per patient (2011 dollars)	ICER compared to IHC only (2011 dollars per additional case detected)
1	Both IHC and MSI in all	10.8	0	1,098	Dominated
2	IHC only in all	9.2	3	532	Referent
3	MSI only in all	5.0	11	1,235	Dominated
4	IHC tested in all, followed by MSI in cases where IHC shows normal expression of all 4 MMR proteins	10.8	0	1,049	31,821
5	MSI in all, followed by IHC in cases where MSI shows low or high status	9.6	2	815	73,477
6	Germline testing for mutations in 4 MMR genes in all (i.e. No tumor-based studies)	5.0	11	3,988	Dominated
MSI status (stable, low, and high) are defined as per NIH consensus criteria as 0%, <30%, or >=30% of the allelic markers shifted, respectively.					
All tumor-based testing strategies (strategies 1-5) are followed by secondary cascade tests including MLH1 promoter methylation, BRAF mutation, and finally confirmatory germline testing for MMR gene mutation in appropriate cases.					
Dominated indicates that the strategy is more costly and/or less effective than the alternative.					

Comparison of detecting CRC patients to be managed as HNPCC, including detection rate, missed cases, and incremental cost-effectiveness ratio (ICER)

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Mandatory DVT Prophylaxis Does Not Reduce Venous Thromboembolic Events in Cancer Patients J. Asaro,[2] A. Groman,[4] A. Aquino,[3] J. Skitzki,[1] J.M. Kane.[1]* *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. University at Buffalo Department of Surgery, Buffalo, NY; 3. University at Buffalo School of Medicine, Buffalo, NY; 4. Roswell Park Cancer Institute-Biostatistics, Buffalo, NY.*

INTRODUCTION: Cancer patients are thought to be at high risk for venous thromboembolic events (DVT/PE). With implementation of electronic order

entry, our tertiary cancer center instituted "mandatory" DVT prophylaxis for all hospital admissions (inpatient and outpatient surgery) beginning in October 2007. Admission orders were not accepted unless DVT prophylaxis was ordered or there was an active opt out by the physician with a stated reason. METHODS: Retrospective review of all DVT/PE events within 30 days of a hospital admission (any inpatient admission (IA) and outpatient surgery (OPS)) in comparable "optional" (1/2005-9/2007) vs. "mandatory" (10/2007-5/2010) DVT prophylaxis order eras. Patient demographics, admission details, type of prophylaxis, and outcome were analyzed. RESULTS: There were 34,120 admissions during the total time period (24,901 IA/ 9,219 OPS); 16,363 for the optional (O) (11,944 IA/ 4419 OPS) and 17,757 for the mandatory (M) (12,957 IA/ 4800 OPS) DVT prophylaxis order eras. The number of DVT/PE events in the O era was 67 (prevalence 0.41%) vs 102 for the M era (prevalence 0.57%), p=0.037. In the DVT/PE patients, DVT prophylaxis had been ordered during the index admission in 65.7% for O vs. 83.3% for M (p=0.008). The type of DVT prophylaxis utilized (unfractionated heparin O 66% vs M 46%; low molecular weight heparin O 23% vs. M 39%) was also similar (p=0.08). There was no difference in potential risk factors for DVT/PE for O vs. M (table 1). There was also no difference between O vs. M for status at DVT/PE diagnosis (outpatient 36% vs 25%, p=0.11) or associated symptoms (73% vs 77%, p=0.62). There were no deaths attributable to DVT/PE in the O era vs 3 deaths in the M era. CONCLUSIONS: Although DVT prophylaxis use improved with "mandatory" ordering, the DVT/PE prevalence in patients admitted to a tertiary cancer center did not decrease. It may be difficult to overcome the surprisingly low baseline prevalence and multiple risk factors in this population.

Table 1.

RISK FACTOR	Optional Era	Mandatory Era	p value
surgery admission	34 (50.7%)	54 (52.9%)	0.394
previous DVT/PE	2 (3.0%)	8 (7.8%)	0.13
central venous catheter	17 (25.4%)	38 (37.3%)	0.13
hypercoagulable	46 (68.7%)	52 (51.0%)	0.13
female	37 (55.2%)	45 (44.1%)	0.158

	N (%)	Hazard Ratio	95% Confidence Interval	P value
Age at diagnosis (mean, SD)	84.4 (3.7)	1.06	1.04-1.08	<0.0005
Male	5217 (38.5%)	1.47	1.23-1.74	<0.0005
Race: White	12185 (90.0%)	Reference		
Race: Black	562 (4.2%)	1.01	0.71-1.44	0.97
Marital Status: Married	5477 (40.5%)	Reference		
Marital Status: Widowed	6420 (47.4%)	1.30	1.08-1.55	0.005
Year of diagnosis: 1992-1995	2679 (19.8%)	Reference		
Year of diagnosis: 1996-2000	2748 (20.3%)	1.00	0.80-1.26	0.26
Year of diagnosis: 2000-2002	4060 (30.0%)	1.05	0.84-1.32	0.65
Year of diagnosis: 2003-2005	4051 (29.9%)	0.89	0.69-1.14	0.36
Stage I	3556 (26.3%)	Reference		
Stage II	5884 (43.5%)	1.17	0.95-1.43	0.13
Stage III	3539 (26.1%)	2.00	1.62-2.47	<0.0005
No adjuvant chemotherapy	11638 (86%)	1.87	1.45-2.42	<0.0005
Frailty	588 (4.3%)	5.53	4.55-6.73	<0.0005
Home oxygen	305 (2.3%)	1.45	1.04-2.04	0.03
Hospitalizations in year prior to diagnosis (mean, SD)	1.44 (0.81)	1.17	1.09-1.26	<0.0005
Emergency Room visits in year prior to diagnosis (mean, SD)	3.68 (4.2)	1.02	1.00-1.03	0.04
Mobility: none	11783 (87.0%)	Reference		
Mobility: Cane/ Walker	1258 (9.3%)	1.03	0.84-1.27	0.76
Mobility: Wheelchair	497 (3.7%)	1.31	0.99-1.73	0.06
Dementia	115 (1%)	2.61	1.82-3.73	<0.0005

SD, standard deviation

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Predictors of Poor Short-term Outcome in Oldest Colon Cancer Patients H.B. Neuman,* J. Weiss, E.S. O'Connor, D.Y. Greenblatt, N.K. LoConte, C.C. Greenberg, M.A. Smith. *University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Introduction: Individuals >80 years of age represent an increasingly large proportion of colon cancer diagnoses. Selecting these patients for elective surgery is challenging due to competing comorbidities and functional limitations. The objective was to identify factors predictive of poor short-term outcome after elective surgery in older colon cancer patients. Methods: Medicare beneficiaries >80 years of age who underwent elective colectomy for stage I-III colon cancer from 1992-2005 were identified from the SEER-Medicare database. Mobility was assessed by use of cane/walker or wheelchair. Frailty was assessed using ICD-9 codes for 12 conditions as defined by John Hopkins' Adjusted Clinical Groups (ACG) case-mix system (e.g. difficulty walking, weight loss, frequent falls, malnutrition, impaired vision, decubitus ulcer, incontinence). Kaplan-Meier survival curves and Cox regression examined 90-day and 1-year overall survival. Results: 13538 patients were identified (Table). Most patients were discharged home (73%), with 22% going to a skilled nursing facility. 11% were readmitted within 30 days. 90-day survival was 93.5% and 1-year survival was 85.6%. Factors associated with poorer 90-day survival include frailty (HR 7.73 [CI 5.97-10.0]), dementia (HR 2.55 [CI1.67-3.9]), older age (HR 1.07 [CI 1.04-1.09]), male (HR 1.47 [CI 1.14-1.88]), and more hospitalizations in year prior to diagnosis (HR 1.25 [CI 1.13-1.38]). Additional factors predictive of poorer 1-year survival include use of home oxygen, stage III cancer, no adjuvant chemotherapy, being widowed, and more Emergency Room visits in year prior to diagnosis (Table). In general, specific comorbidities were not associated with poorer outcome. Approximately 4% of patients were considered to be frail. Of these patients, only 59% survived 90-days and 42% survived 1-year after surgery. Discussion: Although most patients >80 years selected for elective colectomy do well, factors reflective of frailty were significantly associated with poorer short term outcomes. Surgeons can use this data to better identify these older patients who may have poor outcomes and who may be better managed by a non-operative approach.

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Outcomes for Metastatic Colorectal Cancer in the Era of Advances in Systemic Therapy and Surgery: A Population-based Analysis D.R. Shah,* W. Tseng, S.L. Chen, S.R. Martinez, R.J. Canter, R.J. Bold, V.P. Khatri. *University of California Davis, Sacramento, CA.*

Introduction: Since the year 2000, there have been considerable advances in the systemic therapies for metastatic colorectal cancer (MCC). There have also been notable improvements in surgical therapy for liver metastases due to advances in surgical and anesthetic techniques, incorporation of technology and use of portal vein embolization. The purpose of this analysis was to compare outcomes for MCC prior to and following these advances using the Surveillance, Epidemiology, and End Results (SEER) database Methods: We queried the SEER database for all patients with MCC diagnosed between 1990 and 2007. Patients were categorized by time period and whether hepatic resection was performed. Exclusions were made for incomplete information. Further data were collected on patient demographics and tumor characteristics. Univariate overall survival comparisons were made using the Kaplan Meier method, while multivariate comparisons were performed using the Cox proportional hazards regression adjusting for age, race, sex and geographic location. Results: 70,508 patients met the criteria for analysis. 25,795 were diagnosed between 1990-1999 (Period 1) and 44,713 from 2000-2007 (Period 2). Liver resection was performed in 903 (3.5%) of the Period 1 population and 1980 (4.4%) in Period 2. There were significant variations in the outcomes by the patient's geographic region. Overall the median survival of patients with MCC was significantly better in Period 2 (10 mth vs 13mth, p<0.0001). Furthermore, compared to Period 1, there was also significant improvement in the group that underwent hepatic resection (15mth vs 21mth). On multivariate analysis, this difference persisted after adjusting for age, race, gender, geographic location with a hazard ratio of 0.729 (CI 0.69-0.76) favoring hepatic resection and a hazard ration of 0.87 (0.86-0.89) favoring treatment in period 2 (2000-2007). Conclusions: Our analysis demonstrated significant improvement in outcomes for multiple subgroups of patients with MCC treated in the post-2000 era. Although these data are observational, they support the hypothesis that the overall prognosis of MCC is improving.

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Does Geography Influence the Treatment and Outcomes of Colorectal Cancer in the Province of Manitoba? R.M. Helewa,[1]* D. Turner,[2] D. Wirtzfeld,[1] J. Park,[1] E. Shu,[2] L. Xue,[2] A. McKay.[1] *1. University of Manitoba, Winnipeg, MB, Canada; 2. CancerCare Manitoba, Winnipeg, MB, Canada.*

Background: The Province of Manitoba covers a huge geographical area, but has one large urban center, Winnipeg. Over a third of the population must travel considerable distances to access specialized medical care. We sought to determine if regional differences exist in quality of care and outcomes for colorectal cancer in a publically funded health care system. Methods: This was a population-based historical cohort analysis of the treatment and outcomes of all patients diagnosed with colorectal cancer in Manitoba between 2004 and 2006. The Manitoba Cancer Registry and administrative data from Manitoba Health were utilized to assess quality of care taken from published quality indicators. Results: 2,086 patients were diagnosed with Stage I-IV colorectal cancer and 1,628 underwent surgery. The mean age of diagnosis was 70 years, 53.8% of patients were male, and 42.2% lived outside of Winnipeg. For patients who underwent surgical resection, there were no differences between Winnipeg and rural Manitoba patients in the quality indicators of 30-day operative mortality, perioperative total colonic examination, anastomotic leak rate, extent of lymphadenectomy, and post-operative surveillance colonoscopy (Table 1). For rectal cancer, there were no differences in rates of preoperative consultation with radiation and medical oncology. For stage III colon cancer, rates of consultation with medical oncologists within 8 weeks of surgery did not differ. There were higher rates of preoperative radiological evaluation in Winnipeg and surveillance CT/MRI within 1 year of surgery. Conclusion: Compliance rates with certain quality indicators for treatment of colorectal cancer in Manitoba are low. However, there appear to be minimal differences according to geography, despite the significant travel that is often required. This study is one of the few studies to establish population-based benchmarks for colorectal therapy in Canada.

Table 1: Quality Measures for Colorectal Cancer with Variation by Geography

	Geographic Variation		
Quality Measure	Winnipeg	Other	P-Value
30 Day Mortality	4.1%	3.3%	0.506
Total Colonic Examination	75.1%	76.2%	0.604
Preoperative Radiological Evaluation	18.3%	12.9%	0.0033
Anastomotic Leak Rate	2.2%	1.1%	0.168
Extent of Lymphadenectomy (12+ LN)	69.1%	68.3%	0.749
Preoperative Consultation with Medical Oncology for Rectal Cancer	12.9%	13.5%	0.866
Stage II/III Rectal Cancer seen within 8 weeks of surgery by Medical Oncology	37.2%	34.7%	0.693
Preoperative Consultation with Radiation Oncology for Rectal Cancer	18.4%	16.9%	0.706
Stage II/III Rectal Cancer seen within 8 weeks of surgery by Radiation Oncology	33.8%	27.4%	0.294
Stage III colon cancer seen within 8 weeks of surgery	27.4%	27.2%	0.966
Surveillance Colonoscopy within 1 year of surgery	27.1%	25.5%	0.496
Surveillance CT/MRI within 1 year of surgery	66.5%	50.7%	<0.0001

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Is Treating Pancreatic Head Adenocarcinoma Too Costly? Cost-effectiveness and Opportunities for Improvement D.E. Abbott,[1]* R.P. Merkow,[2] S.B. Cantor,[1] J.B. Fleming,[1] G.R. Varadhachary,[1] C.. Crane,[1] D.J. Bentrem,[3] K.Y. Bilimoria.[3] *1. Surgical Oncology, MD Anderson Cancer Center, Houston, TX; 2. American College of Surgeons, Chicago, IL; 3. Northwestern University/Feinberg School of Medicine, Chicago, IL.*

Background Dismal long-term survival has led many practitioners to have a nihilistic attitude toward treating pancreas cancer. As fiscal constraints increasingly impact healthcare delivery, this study was designed to examine the cost-effectiveness of various treatment strategies for resectable pancreatic head adenocarcinoma and identify opportunities for cost reduction. Methods A decision model was constructed to compare 6 strategies: surgery plus adjuvant therapy, surgery alone, chemotherapy plus radiation, radiation alone, chemotherapy alone, and no treatment. The NCDB, ACS NSQIP, and literature were used to identify probabilities of stage-specific treatment and outcomes. Cost data were estimated using Medicare reimbursement (2011$). Incremental cost-effectiveness ratios (ICERs) and sensitivity analyses were based on varying key parameters of the model (e.g. probabilities associated with care at low- vs. high-performing centers). Survival was reported in quality-adjusted life months (QALM). Results The strategies of radiation alone and surgery alone were dominated (more costly and less effective) by at least one other strategy. Chemotherapy, chemotherapy plus radiation, and surgery plus adjuvant therapy demonstrated ICERs (compared to the next least costly alternative) of $3022/QALM, $14,844/QALM, and$23,920/QALM, respectively. Theoretically increasing survival of node- and margin-negative patients from 14 to 22 months had the largest impact in reducing the cost of surgery ($17,113/QALM). Sensitivity analysis using probability data from low- and high-performing centers revealed that high-performing centers possessed a significantly lower ICER for the addition of surgery to adjuvant chemoradiation: $15,503 vs. $51,982 per QALM. Conclusion Surgical therapy for resectable pancreatic head adenocarcinoma extends survival, but at considerable cost. However, significant cost reductions could be realized if treatment and outcomes were improved to the level of high-performing centers. Because extending survival is a powerful modulator, increasingly effective chemotherapeutic agents would also greatly improve the cost-effectiveness of treating pancreatic cancer.

Cost-effectiveness of treatment strategies in resectable pancreatic head adenocarcinoma. (ICER=incremental cost-effectiveness ratio, QALM=quality adjusted life months)

Strategy	Cost (2011 U.S. dollars)	Effectiveness (QALM)	ICER (Cost per additional QALM, 2011 dollars)
No Treatment	692	2.7	--
Radiation therapy	12,351	4.8	Dominated
Chemotherapy	10,361	5.9	3,022
Chemotherapy and radiation therapy	22,236	6.7	14,844
Surgery alone	82,490	6.8	Dominated
Surgery and adjuvant chemotherapy +/- radiation	107,117	10.2	23,920

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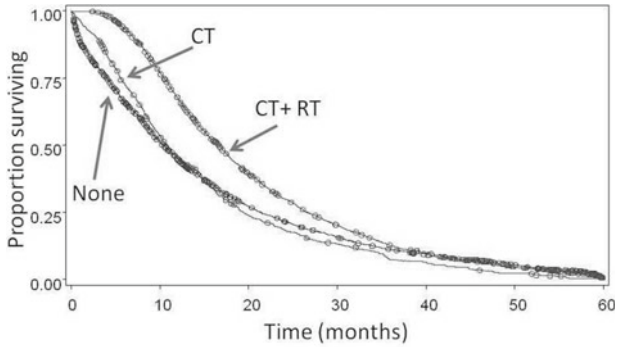
Adjuvant Radiation Plus Chemotherapy is Associated with Improved Survival in Pancreatic Cancer: An Early Analysis of the National Cancer Database D. Kooby,[1]* T. Gillespie,[1] J. Byrd Sellers,[2] J. Bian,[1] J. Lipscomb.[1] *1. Emory, Atlanta, GA; 2. Atlanta VAMC, Atlanta, GA.*

INTRODUCTION: Impact of adjuvant radiotherapy (RT) when added to chemotherapy (CT) for pancreatic adenocarcinoma (PAC) remains controversial. We examined effects of adjuvant therapy on overall survival (OS) in PAC, using the National Cancer Database (NCDB), which provides greater detail on therapy than the Surveillance, Epidemiology and End Results (SEER) database, and represents a larger percentage of new U.S. cancer cases yearly (~70% vs. ~30%). METHODS: All patients with resected PAC from 1998-2002 were queried from the NCDB. Receipt of adjuvant therapy was assessed. Cox proportional hazards modeling was used to examine effects of adjuvant therapy type on OS, controlling for hospital type, patient, disease and treatment factors. Factors associated with receipt of any adjuvant therapy were investigated through binary logistic modeling. RESULTS: From 1998-2002, 6167 analyzable patients underwent resection of PAC. Of these, 659 (10.7%) received CT alone, 2841 (46.1%) received CT and RT (CT+RT), and 2667 (43.2%) had no adjuvant therapy (NONE). Three and 5 year survival for all patients were 15% and 7%, respectively. Median OS was 12 months for CT only, 18 months for CT+RT, and 12 months for NONE (see figure). In the multivariable survival analysis, hazard ratios for death were lower for patients with node negative (0.75, $p<0.01$) cancers, treated at NCI programs (0.81, $p<0.01$), who received Chemo and RT (0.68, $p<0.01$). As compared with patient in the NONE group, patients who received any adjuvant therapy were more likely to have node positive (68% CT + RT vs. 67% CT vs. 54% NONE, $p<0.0001$) and margin positive disease (29% CT + RT vs. 31% CT vs. 23% NONE, $p<0.0001$). CONCLUSIONS: Five-year survival for resected PAC remains dismal, and only 58% of patients undergoing pancreatic cancer resection during the time of this study received adjuvant therapy. Despite having a higher incidence of node and margin positive disease, the CT + RT group had the best survival as compared with CT only or NONE. RT as a component of adjuvant therapy appears to confer a survival benefit for patients with resected pancreatic cancer.



Kaplan-Meier Survival curves for resected pancreatic cancer patients who received adjuvant chemotherapy (CT), chemotherapy plus radiation (CT +RT), or no adjuvant therapy (NONE).

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Management of Bowel Obstruction in Patients with Stage IV Cancer: Predictors of Outcome after Surgery V. Francescutti,[1]* Y. Wu,[1] A. Miller,[3] Y. Satchidanand,[2] A. Alvarez-Perez,[2] K. Bullard Dunn.[4] *1. Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. Department of Palliative Care, Roswell Park Cancer Institute, Buffalo, NY; 3. Department of Biostatistics, Roswell Park Cancer Institute, Buffalo, NY; 4. Department of Surgery, Louisville, KY.*

Introduction: Patients with Stage IV cancer and bowel obstruction (BO) present a complicated management problem. A surgical procedure may provide good palliation, but may be associated with morbidity in patients with a limited life span. We sought to determine if specific parameters could predict outcome after surgery. Methods: We reviewed records of patients with Stage IV cancer and BO treated from 1992-2008. For surgical patients, 30-day morbidity/mortality was assessed. Wilcoxon Rank Sum/Pearson Chi Square tests were used. Results: Of 191 patients with Stage IV cancer and BO, 145 (76%) underwent surgery, and 46 medical treatment. 150 had 1 admission for BO (79%); 34 (18%) 2 admissions, and 6 (3%) had > 3. Fifty four patients (28%) were diagnosed with Stage IV disease and BO concurrently. The remaining presented with a BO after diagnosis of Stage IV disease. Demographics were similar for patients who underwent surgery vs those who did not. Medically managed patients were more likely to have received chemotherapy in the 30 days prior to BO [33/46 (71%) vs 48/145 (33%), p <0.01]. In the surgical group, 30-day morbidity was 32%, was higher in those transferred from another facility (n=10) vs those from home (n=135; OR=5.5, p<0.01), and in those with lower serum albumin (p=0.03). 30-day mortality in surgical patients was 10%, more common in those with poor ECOG status (OR=3.9, p<0.01). Median overall survival from date of presentation with BO for surgical patients was 55.5 days (range 42.0-70.0), vs 36.5 days (range 19.0-44.0) for those treated medically. A multivariate proportional hazards model demonstrated that ascites (HR=1.6, CI 1.1-2.3, p=0.06), ECOG ≥ 2 (HR=2.1, CI 1.4-3.1, p<0.01), and male gender (HR=1.6, CI 1.1-2.3, p=0.02) were associated with poor prognosis. Conclusions: This large cohort identifies characteristics indicative of 30-day morbidity/mortality in patients with Stage IV cancer and BO. While surgical patients had longer survival than those treated medically, ascites, ECOG ≥ 2, and male gender were associated with poor surgical outcome. These data suggest specific factors that can be used to frame treatment discussions.

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Utilization of Sentinel Lymph Node Biopsy in Patients with Ductal Carcinoma In Situ Undergoing Mastectomy D.R. Shah,* R.J. Canter, V.P. Khatri, R.J. Bold, S.R. Martinez. *Surgery, University of California Davis, Sacramento, CA.*

Background: Current National Comprehensive Cancer Network guidelines suggest consideration of sentinel lymph node biopsy for patients with DCIS undergoing mastectomy. Our objective was to evaluate factors influencing the utilization of sentinel lymph node (SLN) biopsy in patients receiving mastectomy for the treatment of DCIS. Methods: We used the Surveillance Epidemiology and End Results (SEER) database to identify all female patients with breast DCIS treated with mastectomy from 2000 to 2008. Exclusions were made for patients without histologic confirmation, including those diagnosed at autopsy. Furthermore, we excluded patients who had axillary lymph node dissections completed for axillary staging and those for whom the status of SLN surgery was unknown. Univariate and multivariate logistic regression evaluated the relationship of patient and tumor-related factors on the likelihood of undergoing SLN biopsy. We used odds ratios (OR) and 95% confidence intervals (CI) to identify significant associations. Results: Entry criteria were met by 20,177 patients. Approximately half (51%) of the patients did not receive SLN biopsy. Factors associated with a decreased likelihood of receiving a SLN biopsy included advancing age (OR 0.64, CI 0.60-0.69), Asian (OR 0.76, CI 0.68-0.86) and Hispanic (OR 0.82, CI 0.70-0.96) race, patients for whom their DCIS was not their first or only primary tumor (OR 0.55, CI 0.51-0.60), and patients treated in the Midwest (OR 0.88, CI 0.78-0.99) and South (OR 0.83, CI 0.73-0.94). Factors associated with an increased likelihood of receiving a SLN biopsy included patients treated in the East (OR 1.20, CI 1.07-1.35), patients with grade II (OR 1.27, CI 1.11-1.48), III (OR 1.94, CI 1.68-2.25), or IV (OR 2.17, CI 1.85-2.54) tumors, patients treated after the year 2000, and those with T2 (OR 1.17, CI 1.08-1.28) and T3 (OR 1.20, CI 1.05-1.36) tumors. Conclusions: SLN biopsy is under-utilized in patients with DCIS undergoing mastectomy. Future efforts at improving rates of SLN biopsy in this population are warranted.

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Factors Associated with Breast Symmetry after Breast Conserving Surgery for Cancer H. Medina-Franco,* P. Rojas-García, Y.L. Suárez-Bobadilla. *National Institute of Medical Sciences and Nutrition "Salvador Zubiran", Mexico City, DF, Mexico.*

Breast-conserving surgery (BCS) is the standard of care for treatment of early breast cancer. Many patients report breast asymmetry after BCS. Factors associated with poor cosmetic results are not well described. The aim of the present study was to evaluate factors associated with breast symmetry after BCS for invasive breast cancer. Methods: Patients who underwent unilateral BCS for invasive breast cancer and completed at least six months after radiation therapy were included. After informed consent, patients answered a validated questionnaire for breast symmetry. Demographic, clinical, pathological, surgical and radiation therapy variables were recorded. Bilateral breast volume was measured in office and volume difference >20% was considered objective asymmetry. Variables were analyzed with chi-square test and significance was considered at p<0.05. Results: Three-hundred and thirty-three patients were included. Mean patient age was 56 ±9 years. Most patients were married (78%) with educational level of high school or greater (50.8%). Mean body mass index (BMI) was 25±8. Right breast was more commonly affected (61%) as well the upper outer quadrant (67%). Seventy-eight percent of patients underwent only one surgical procedure and 12% two or more. Eighty-one percent of patients had tumors > 1cm. Surgical morbidity was low (4.7%)- mainly seroma formation. Twenty-two percent of patients had objective asymmetry and 27% perceived themselves with asymmetry according to questionnaire. There were no significant relationship between objective and subjective asymmetry (p>0.05). The only variables significantly associated with perception of breast asymmetry were BMI ≥25 and educational level ≥ high school. There was no significant association with other variables like tumor size or number of surgical procedures. Conclusions: There was no relationship between subjective and objective breast asymmetry after BCS, suggesting that cosmetic results are mainly related to patient subjective perception. The only variables associated with breast asymmetry were overweight and high education, possibly because higher cosmetic expectations in this last group of patients.

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Surgical Oncology Fellowship Graduates: What Are They Doing Now? R. Wiatrek,[1]* W. Lee,[1] C. Wray,[2] G. Singh,[1] J. Yim,[1] J. Garcia-Aguilar,[1] S.L. Chen,[1] J. Kim.[1] *1. City of Hope National Medical Center, Duarte, CA; 2. The University of Texas Health Science Center, Houston, TX.*

INTRODUCTION: As surgical oncology training transitions to Accreditation Council for Graduate Medical Education (ACGME) specialty certification, an assessment of the roles that surgical oncologists fill in contemporary surgical practices may be necessary. We sought to examine the type of clinical practices that surgical oncology fellowship graduates currently maintain. METHODS: Practice data was gathered for surgeons who completed Society

of Surgical Oncology (SSO)-approved surgical oncology fellowship programs between 2003-2008. Types of practice were defined as: (1) University Hospital Centers (UHC) or NCI-designated Cancer Center (NCICC); (2) University-affiliated hospital with resident training programs (UAH); (3) Community hospital with residency training program (ComRT); (4) Private practice; (5) Military; and (6) International. RESULTS: Of 253 surgeons who matched into SSO approved programs during our study period, 10 had not completed training, 11 entered military positions, and 17 were practicing internationally. Of the remaining 215 surgeons, 75% (n=161) obtained teaching positions and 25% (n=54) entered private practice. Of those in teaching positions, the majority were at UHC/NCICC (n=133); followed by UAHs (n=16) and ComRTs (n=12). Overall, the practice focus was most commonly general surgical oncology (60%, n=130) followed by hepatopancreatobiliary (HPB) (20%, n=43), breast/endocrine or melanoma/sarcoma (17%, n=36), and breast alone (3%, n=6). CONCLUSION(S): Our study shows that a large majority of fellows obtain teaching positions and have a general surgical oncology practice. For those with a subspecialty focus, HPB was the most commonly followed by a combination of breast, endocrine, melanoma and sarcoma. Core requirements for an ACGME accredited surgical oncology fellowship should consider the practice patterns of program graduates.

ABSTRACTS

Accepted for
POSTER PRESENTATIONS

65th Annual Cancer Symposium
Society of Surgical Oncology
March 21-24, 2012
Orlando, Florida

P1

CCR2 Signaling Inhibition Improves Tumor Control in Pancreatic Cancer J. Mitchem,* D. Sanford, M. Porembka, G. Lin, S.P. Goedegebuure, D.C. Linehan. *Department of Surgery, Washington University School of Medicine, St Louis, MO.*

Pancreatic adenocarcinoma (PA) is notoriously aggressive and difficult to treat. One major reason for this is the highly pro-tumor microenvironment induced by PA. One key component of this tumor microenvironment are myeloid cells recruited from the bone marrow that play important roles in tumor induced immune suppression, angiogenesis and invasion/metastasis. The CCL2/CCR2 signaling axis is key for the recruitment of myeloid cells to the tumor microenvironment, which makes this an attractive target in PA. In this study we show that CCR2/CCL2 signaling inhibition improves primary tumor control and can be effectively targeted using a novel CCR2 antagonist. The Oncomine database (oncomine.org) was used to compare CCL2 expression in normal pancreas and PA. The Pan02 PA cell line was injected subcutaneously (SQ) into CCR2-/- mice and wild type (WT) C57BL/6 for comparison and drug treatment. Tumor growth was measured by caliper method. Tumor tissue was obtained from mice in each group and subjected to flow cytometric analysis. A small molecule CCR2 antagonist (CCR2i) was obtained from Pfizer Corporation, and utilized at 20mg/kg/day SQ in divided doses BID for treatment studies. Analysis showed CCL2 expression is upregulated in human PA, as well as in the Pan02 pancreatic tumor model. To investigate CCR2 signaling inhibition, 8-10 week old WT and CCR2-/- mice were inoculated with the Pan02. Tumors grew significantly slower, and survival was prolonged in CCR2-/- mice when compared to WT mice(Fig 1A). Pharmacological inhibition of CCR2 using CCR2i in tumor-bearing mice resulted in significantly decreased tumor growth(Fig 1B). Analysis of CCR2i treated tumors at Day 28 of treatment showed decreased infiltration of tumor associated macrophages (TAM) and monocytic myeloid derived suppressor cells (mo-MDSC). Additionally, Regulatory T cells (Treg) were decreased, and CD4 and CD8 T cells were increased, suggesting an immune mechanism. Novel therapeutic targets are of the upmost importance for the treatment of PA. In this study we show that the CCL2/CCR2 signaling axis is important for PA growth and that this axis can be targeted effectively using a small molecule CCR2 antagonist.

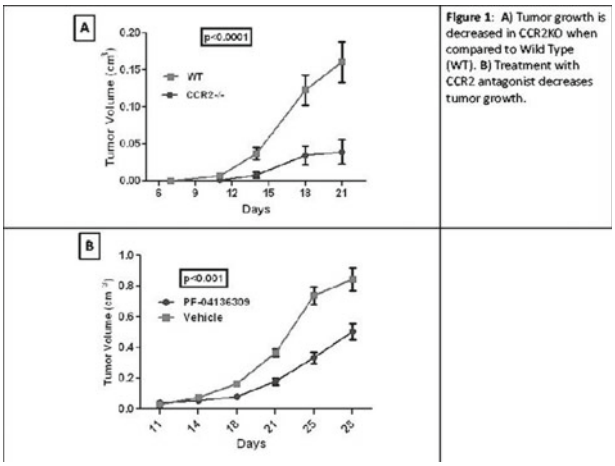
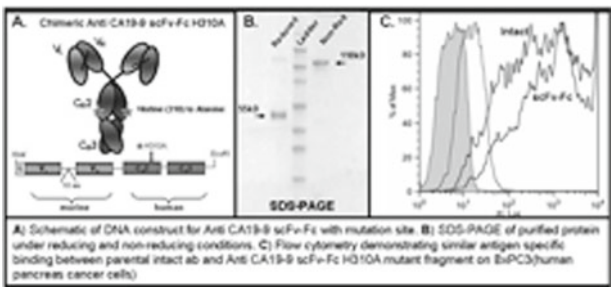


Figure 1: A) Tumor growth is decreased in CCR2KO when compared to Wild Type (WT). B) Treatment with CCR2 antagonist decreases tumor growth.

P2

An Engineered Chimeric, Fc Mutated, Anti-CA19-9 scFv-Fc for Imaging Pancreas Cancer M.M. Rochefort,[1]* M.D. Girgis,[1] S. Knowles,[2] F. Bergara,[2] T. Olafsen,[2] J.S. Tomlinson.[3] *1. UCLA, Department of Surgery, Los Angeles, CA; 2. UCLA, Department of Molecular and Medical Pharmacology, Crump Insitute for Molecular Imaging, Los Angeles, CA; 3. Veterans Affairs, Greater Los Angeles, Department of Surgery, Los Angeles, CA.*

Introduction: Antibody based tumor targeting has the potential to provide improved imaging as well as targeted therapy. CA19-9, a carbohydrate tumor antigen present on over 90% of pancreatic cancers, is a suitable candidate for antibody targeting. Intact murine antibodies have major shortcomings that inhibit direct translation as an imaging agent; long serum persistence results in high background signal and murine proteins are immunogenic. Engineering of chimeric antibody fragments serves to decrease the immunogenicity and mutations in the Fc region can dramatically reduce serum persistence. We sought to develop a chimeric, Fc mutated, Anti-CA 19-9 antibody fragment (Anti-CA 19-9 ScFv-Fc H310A) to improve upon our previous work utilizing radiolabeled intact CA19-9 antibody microPET imaging of pancreas cancer xenografts. **Methods:** Anti-CA19-9 scFv-Fc H310A DNA construct was created utilizing the murine variable regions(V_h and V_l) from the parental intact Ab(1116-NS-19-9) linked to a human IgG1 Fc region, ligated into a mammalian expression vector and expressed in NS0 cells. High protein producing clones were identified by western blot and expanded. Our fragment was purified from supernatant using a ProteinG column. Further biochemical characterization of our pure protein was performed utilizing size exclusion chromatography, SDS-PAGE, Western Blot and flow cytometry. **Results:** The chimeric Anti-CA19-9 ScFv-Fc H310A was successfully expressed by NS0 cells and purified on a ProteinG column. SDS-PAGE revealed a 110 kD dimer (nonreduced) and a 55kD monomer (reduced). Western blot confirmed that both protein bands were labeled with an anti human Fc antibody. Size exclusion chromatography shows an elution time of ~27 minutes, consistent with prior published data on scFv-Fc fragments. Flow cytometry demonstrated antigen specific binding of CA19-9 positive cells comparable to the intact CA19-9 antibody. **Conclusion:** We successfully engineered and produced a chimeric Anti-CA 19-9 ScFv-Fc H310A fragment that retains similar antigen specific binding affinity when compared to the parental intact murine antibody. Future work will evaluate in vivo targeting of pancreas cancer xenografts



A) Schematic of DNA construct for Anti CA19-9 scFv-Fc with mutation site. B) SDS-PAGE of purified protein under reducing and non-reducing conditions. C) Flow cytometry demonstrating similar antigen specific binding between parental intact ab and Anti CA19-9 scFv-Fc H310A mutant fragment on BxPC3(human pancreas cancer cells)

P3

Axl Receptor Tyrosine Kinase is Essential to Pancreatic Tumor Progression and Metastases A.R. Kirane,* M.T. Dellinger, K.T. Ostapoff, J.E. Toombs, R.E. Schwarz, R.A. Brekken. *UTSW, Dallas, TX.*

Expression of receptor tyrosine kinase Axl in pancreatic cancer is associated with increased metastasis and shorter survival. Axl has been identified as participating in invasion and transformation, but precise function of Axl in pancreatic cancer is ill-defined. Gas6, the Axl ligand, is inhibited potently by warfarin at doses lower than required for anticoagulation. Here, we investigate Axl as a novel target in treatment of pancreatic cancer. Cell lines used for study included stable Axl knockdown, 1132, generated from parental MiaPaCa2 cells, Axl+ cells AsPC-1, Panc-1, C5LM2, and Axl- Capan-1. In vitro function was assessed by anchorage independent growth, gemcitabine sensitization and migration. All cell lines were implanted orthotopically into SCID mice, Pan02 murine cells were implanted in C57BL/J6 mice. Warfarin began on post-implantation day 7. Inhibition of Axl resulted in dramatically reduced colony formation in soft agar and migration for Axl+ cells. Warfarin treatment reduced the IC50 of gemcitabine proportionally to level of Axl expression. 1132 tumor bearing animals had no discernable tumors at 58 days, while control mice were significantly moribund. At day 72, half of 1132 animals had developed tumors. IHC and qPCR analysis demonstrated high Axl in tumors that grew, those that failed to progress showed no Axl, suggesting growth required recovery of Axl. Metastases were significantly lower in all 1132 animals. Panc-1 and AsPC-1 tumors were smaller in warfarin treated animals, but this was not significant, but metastatic incidence was profoundly decreased. Tumor size and metastases were equal amongst Capan-1 groups. Pan02 tumors were significantly smaller and metastases were not observed with warfarin. Panc-1 tumor lysates demonstrated inhibition of Axl signaling with warfarin via decreased phosphorylation of Akt and Erk. We conclude that Axl function is critical in the progression of pancreatic cancer. Inhibition of Axl signaling with subtherapeutic warfarin resulted in a reduction of metastases for Axl expressing tumors and

sensitized cells to gemcitabine in vitro. This finding warrants further evaluation of Axl as a novel target to augment chemotherapy.

P4

Toll-Like Receptor Signaling Promotes Lymphatic Repair following Tissue Injury and Lymphatic Disruption J.C. Zampell,* A. Yan, T. Avraham, E. Weitman, S. Del Vecchio, B.J. Mehrara. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Mechanisms regulating lymphedema pathogenesis are unknown. We have shown that activation of endogenous danger signals in response to lymphatic fluid stasis contributes to lymphangiogenesis; however, the role of cognate toll-like receptors (TLRs) in this process remains undefined. The purpose of this study was to determine the effect of TLR loss in the development and progression of lymphedema following lymphatic disruption. Methods: A mouse tail model of lymphedema was used in which superficial and deep lymphatics were disrupted to induce lymphedema progression over 12 weeks. Operations were performed in wild-type mice or TLR2, TLR4, and TLR9-deficient mice, and animals were sacrificed after 6 weeks. Tail volume and dermal thickness were measured to determine lymphedema progression. Lymphatic function was assessed by microlymphangiography and histologic analysis of vessel morphology and number. Inflammation and fibrosis were evaluated by immunohistochemistry. Results: Loss of TLR function led to increased tail volume (50-200% increase, $p<0.01$) and dermal thickness (45%-87% increase, $p<0.001$). These findings correlated with reduced lymphatic flow across the region of lymphatic disruption, increased dilation of capillary lymphatics (3-fold increase, $p<0.05$), and reduced numbers of podoplanin positive dermal capillary lymphatics in TLR KO (50-60% reduction, $p<0.05$ for TLR4 knockout (KO)) compared to wild types. TLR KOs demonstrated an altered inflammatory response, characterized by increased leukocytes (67% higher CD45 infiltrate, significant in TLR4 KOs, $p<0.05$) and reduced macrophage infiltration (29-59% reduction, $p<0.05$) compared to wild types. These findings correlated with increased collagen deposition (2-fold increase, significant for TLR4 KOs, $p<0.05$) and tail fibrosis in TLR KO mice. Conclusion: These results show that TLR deficiency leads to worsened lymphatic regeneration. Lymphatic dysfunction furthermore correlates with increased inflammation and fibrosis following TLR4 loss. These findings suggest that TLRs promote lymphatic repair to restore lymphatic fluid flow following tissue injury and lymphatic disruption.

P5

Perioperative Sepsis, but Not Hemorrhagic Shock, Promotes the Development of Cancer Metastases in a Murine Model R. Seth,[1]* L. Tai,[1] T. Lam,[1] T. Falls,[1] C. Souza,[1] J. Bell,[1] H. Atkins,[1] R. Boushey,[2] R. Auer.[1] *1. Center for Innovative Cancer Research, The Ottawa Hospital Research Institute, Ottawa, ON, Canada; 2. Department of Surgery, Division of General Surgery, The Ottawa Hospital - General Campus, Ottawa, ON, Canada.*

Background: Surgery is thought to promote cancer metastases. Although sepsis and blood loss are associated with poorer outcomes in cancer patients, mechanisms by which they increase tumor metastases are incompletely understood. We hypothesize that the combination of surgery and perioperative complications, involving sepsis and blood loss, may further enhance postoperative metastases. We sought to establish a murine model of surgical stress involving sepsis and blood loss to study their effects on postoperative cancer metastases. Methods: Surgical stress was induced by partial hepatectomy (PH) or left nephrectomy (LN) preceded by an intravenous challenge of CT26LacZ colon cancer cells in Balb/c mice or B16LacZ melanoma cells in C57Bl/6 mice to establish pulmonary metastases. Sepsis was induced by puncturing the cecum with an 18G needle and expressing stool into the abdomen. Hemorrhagic shock was induced by removal of 30% of total blood volume via saphenous vein. Lung tumor burden was quantified at 3 days post intervention. Results: Surgical stress (PH) resulted in a two-fold increase in metastases compared to non-surgery mice in both murine models (Balb/c and C57Bl/6). Mice that received anesthesia only had a lung tumor burden equivalent to untouched controls. LN also significantly increased metastases to a similar degree as PH. The prometastatic effect of surgery was further augmented in mice subjected to perioperative sepsis resulting in a further two-fold increase in metastases. In contrast, surgically stressed mice subjected to Stage 3 hemorrhagic shock did not show an additional increase in their lung tumor burden. Conclusions: Surgical stress induced by two different means results in a two-fold increase in lung tumor metastases in two different murine model systems. Sepsis, but not hemorrhagic shock results in further augmentation of cancer metastases. Further studies aimed at exploring immune suppression as a key mechanism is being actively pursued. This will be important in the future development of perioperative immunomodulation strategies aimed at attenuating metastatic disease in the setting of sepsis and blood loss.

P6

Lymphatic Stasis Activates Expression of Fat Differentiation Genes E. Weitman,* S. Aschen, J.C. Zampell, S. Elhadad, M. De Brot, B.J. Mehrara. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

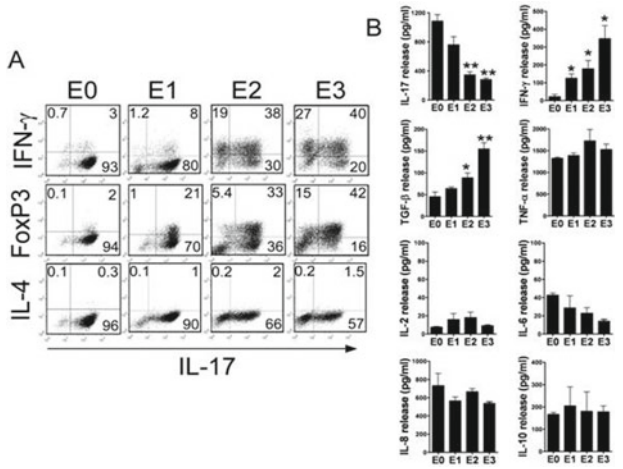
Introduction: Fat deposition is one of the defining characteristics of lymphedema; however, the cellular mechanisms underlying this phenomenon remain unclear. The purpose of this study was to assess how lymphatic fluid stasis regulates fat deposition and adipogenic differentiation. Methods: Microsurgical disruption of the superficial and deep lymphatics of mouse tails was performed to induce lymphatic fluid stasis and resultant lymphedema. Animals were sacrificed 1, 3 or 6 weeks post-operatively (n=8/group). Samples were analyzed for fat differentiation markers by immunohistochemical staining and western blot. An additional group of mice underwent axillary dissections (ALND) or sham incisions and upper extremity tissues were harvested at 3 weeks post-operatively (n=8/group). Results: Lymphatic fluid stasis resulted in significant subcutaneous fat deposition and fibrosis in lymphedematous tail regions ($p<0.001$). Western blot analysis demonstrated that proteins regulating adipogenic differentiation genes including CCAAT/enhancer binding protein-alpha (CEBP-α) and adiponectin were markedly upregulated in the setting of lymphatic fluid stasis. Expression of these markers increased along a spatial gradient of lymphatic stasis, seen most prominently in regions distal to the wound. We found similar changes in CEBP-α and adiponectin expression in tissues harvested after ALND as compared with sham incision. Immunohistochemical localization demonstrated that adiponectin and peroxisome proliferator-activated receptor gamma (PPAR-γ), another adipogenic transcription factor, were expressed by a variety of cell types including fibroblasts, endothelial cells and inflammatory cells. Conclusions: The mouse-tail model of lymphatic fluid stasis demonstrates pathological findings similar to clinical lymphedema including fat deposition and fibrosis. Lymphatic fluid stasis potently upregulates the expression of fat differentiation genes both spatially and temporally in a variety of cell types. This study establishes a foundation for understanding the regulation of abnormal fat deposition in lymphedema pathogenesis, which may ultimately provide a basis for developing targeted treatments for lymphedema.

P7

Role of Th17 Cells in the Tumor Suppressive Microenvironment E.C. Hsueh,* J. Ye, C. Ma, Y. Zhang, D.F. Hoft, G. Peng. *Dept of Surgery, Saint Louis University, St. Louis, MO.*

Although Th17 cells play critical roles in the pathogenesis of many inflammatory and autoimmune diseases, their functional role in human tumor immunity remains largely unknown. We have recently identified Th17 cells as an important component of human tumor-infiltrating lymphocytes (TILs) obtained from melanoma, breast, colon and ovarian cancer patients, but their stability and plasticity in the tumor microenvironment is still unclear. Tumor-infiltrating lymphocytes (TILs), tumor cells and tumor-derived fibroblast were generated from fresh tumor tissues of melanoma, breast cancer and colon cancer. The percentage of Th17 cells in TILs was analyzed by FACS analysis of IL-17 intracellular staining in CD4+ T cell population. Th17 cells were stimulated with OKT-3 and peripheral blood mononuclear cells. FocP3 and IFN-gamma were determinined by FACS. RT-PCR was performed to analyze mRNA expression of cytokines and lineage-specific transcription factors. Th17 clones were generated from tumor-infiltrating T lymphocytes (TILs). Th17 clones can differentiate into IFN-gamma-producing and FoxP3+ cells after in vitro stimulation with OKT3 and allogeneic peripheral blood mononuclear cells (PBMCs) (Figure 1). Lineage-specific transcriptional factor analysis and cytokine gene expression profile of the Th17 cells showed that T cell receptor (TCR) engagement was responsible for this conversion and that this differentiation was due to the epigenetic modification and reprogramming of gene expression profiles. These differentiated Th17 clones also mediated potent suppressive function after repetitive stimulation with OKT3, suggesting that these Th17 clones had

differentiated into functional Treg cells. These results provide the critical evidence that human Th17 cells can differentiate into Treg cells. These Th17 cells also exhibit developmental plasticity which may have clinical implications for the development of novel cancer immunotherapeutic approaches.



Th17 cells differentiate into IFN-g-producing and FOXP3+ cells after in vitro unbiased TCR stimulation and expansion. (A) IL-17, IFN-g, FOXP3 and IL-4 expression in Th17 clones after each round of stimulation (E1-E3) with OKT3 and PBMCs. (B) Cytokine profiles of expanded Th17 clones.

P8

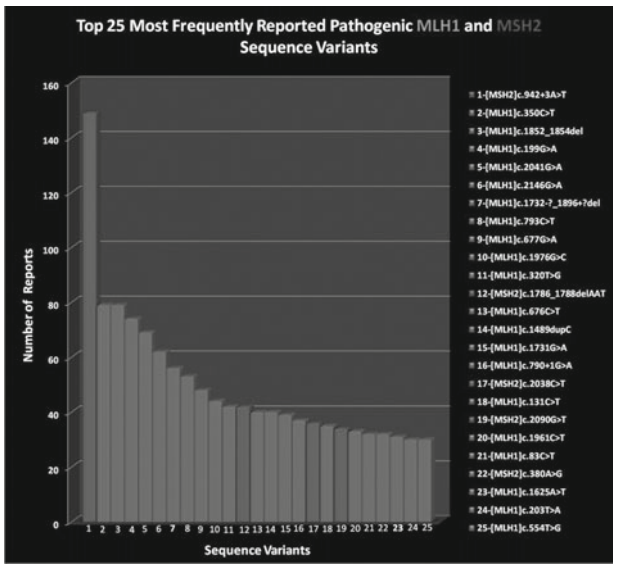
NVP-BEZ235, A Dual PI3K/mTOR Inhibitor, Enhances Chemotherapy and Antiangiogenic Response in Pancreatic Cancer K.T. Ostapoff,* N. Awasthi, P.L. Yen, C. Zhang, M.A. Schwarz, R.A. Brekken, R.A. Schwarz. *Surgical Oncology, University of Texas Southwestern, Dallas, TX.*

The phosphatidylinositol-3-kinase (PI3K)/AKT and mammalian target of rapamycin (mTOR) signaling pathway dysregulation is a prominent feature of pancreatic ductal adenocarcinoma (PDAC). Gemcitabine, a standard systemic treatment for PDAC, has limited clinical benefits. The present study investigated the effects of NVP-BEZ235 (BEZ235), a novel dual PI3K/mTOR inhibitor, in combination with gemcitabine and endothelial monocyte activating polypeptide II (EMAP) in experimental PDAC. Protein expression and cell proliferation were analyzed by Western blotting and WST-1 assay. Animal survival experiments were performed in murine xenografts. BEZ235 inhibited phospho-AKT (Ser473) and phospho-mTOR (Ser2448) expression in PDAC (AsPC-1), endothelial (HUVECs) and fibroblast (WI-38) cells. NVP-BEZ235 also caused a significant dephosphorylation of downstream mTORC1 target proteins phospho-p70 S6K (Thr389) and phospho-4E-BP1 (Thr37/46). In vitro 72-hour proliferation of four PDAC cell lines was significantly inhibited by BEZ235. Additive effects on proliferation inhibition were observed in the BEZ235 and gemcitabine combination in PDAC cells and in combination of BEZ235 or EMAP with gemcitabine in HUVECs and WI-38 cells. BEZ235, alone or in combination with gemcitabine and EMAP, induced apoptosis in AsPC-1, HUVECs and WI-38 cells as observed by increased expression of cleaved poly (ADP-ribose) polymerase-1 (PARP-1) and caspase-3 proteins. PDAC in vivo therapy demonstrated that compared to controls (median survival: 16 days), animal survival increased after BEZ235 and EMAP therapy alone (both 21 days) and gemcitabine monotherapy (28 days). Further increases in survival occurred in combination therapy groups BEZ235+gemcitabine (30 days, p=0.007), BEZ235+EMAP (27 days, p=0.02), gemcitabine+EMAP (31 days, p=0.001) and BEZ235+gemcitabine +EMAP (33 days, p=0.004). BEZ235 has experimental PDAC antitumor activity in vitro and in vivo that can be further enhanced in combination with cytotoxic (gemcitabine) and antiendothelial (EMAP) agents. These findings demonstrate advantages of combination therapy strategies targeting multiple pathways in pancreatic cancer treatment.

P9

Analysis of the InSiGHT DNA Mismatch Repair Gene Database Redefines the Contribution of MSH2 to Global Colorectal Cancer (CRC) Incidence R.P. Raval,[1] J. Plazzer,[2] L.D. Baez-Cabrera,[1] F. Serafini,[1] F. Macrae,[2] T.K. Weber.[1]* *1. State University of New York Surgical Research Unit at VA New York Harbor Medical Center, New York, NY; 2. Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, VIC, Australia.*

Background: We previously reported to this forum an analysis of the International Society for Hereditary Gastrointestinal Tumors (InSiGHT) (www.insight-group.org) mismatch repair (MMR) gene mutation database. Since then a consortium of investigators organized by the Human Variome Project (www.humanvariomeproject.org) has significantly expanded the MMR database (www.lovd.nl). Our current report presents a unique analysis of the contribution of DNA MMR gene sequence variation to CRC incidence. Methods:We manually compiled frequency distribution histograms of all DNA MMR gene sequence variants reported to InSiGHT. Organized by gene, exon, codon and specific nucleotide change we contrasted these results with our previous report. Results:Our analysis demonstrates a dramatic increase in the number of MMR gene sequence variant reports from 884 in 2008 to 12,550 as of August 2011. For MLH 1, 451 unique pathogenic alterations across 1150 reports are now reported compared to, 260 unique alterations across 375 reports in 2008. For MSH2, 382 unique pathogenic alterations across 1090 reports are now noted compared to 180 uniques across only 275 reports in 2008. The sequence variant most frequently reported as pathogenic remains the A to T transversion of MSH2 at base pair 942+3 with 149 reports compared to 22 in 2008. However, only 45% of literature reports associated with this variant support its "pathogenicity". Importantly MSH2 contributes only 5 (20%) of the top 25 most frequently reported pathogenic variants. Of interest, 53% of the 10,606 MSH2 & MLH1 alterations reported were classified as "variants of uncertain clinical significance" Conclusions:Current analysis of the InSiGHT worldwide MMR gene data base documents a 14 fold increase in the number of variants reported compared to 2008. Our results challenge current perception regarding the relative contribution of MLH1 and MSH2 to CRC incidence. These results underscore the success and clinical genetic relevance of the InSiGHT database expansion. However, significant obstacles remain in the interpretation of "pathogenicity" for the most frequently reported alterations.



P10

PG545, A Heparanase Inhibitor, Inhibits Pancreatic Cancer Tumor Cell Proliferation and Migration In Vitro and In Vivo

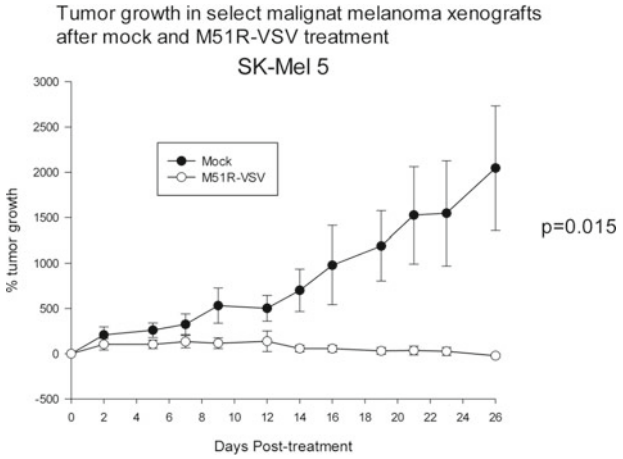
K.T. Ostapoff,* N. Awasthi, R.E. Schwarz, R.A. Brekken. *Surgical Oncology, University of Texas Southwestern, Dallas, TX.*

Introduction: Pancreatic Ductal Adenocarcinoma (PDAC) is highly resistant to conventional chemotherapy, as result there is an ongoing search to find novel effective strategies. Resistance is due in part to the high proportion of stromal tissue within the primary tumor. This intricate ECM (extracellular matrix) includes heparan-sulfate glycosaminoglycans which participate in tumor progression, angiogenesis and metastasis. PG545 is a heparanase inhibitor developed to target these pathways. Methods: In vitro cell viability assays were performed using WST-1 reagent and migration was evaluated using T- scratch assay. Animal survival experiments were performed by intraperitoneal injection of AsPC-1 (0.75 x 10^6) cells. In vivo tumor growth experiments were performed by orthotopic injection of PanO2-HY (5x10^5) cells. Results: PG545 significantly inhibited proliferation of tumor cells (AsPC-1 and PanO2) and fibroblasts (WI-38). PG545 caused only a modest inhibition in endothelial cell (HUVECs) proliferation. Migration was significantly inhibited by 1 μM PG545 in AsPC-1 and PanO2 after 12 hours. In a metastatic model of pancreatic cancer, treatment with PG545 (10 mg/kg 1st week, 5 mg/kg 2nd week) improved survival (35 days) compared to saline (22 days) and gemcitabine (28 days). In an immunocompetent orthotopic model, mice treated with PG545 (5 mg/kg twice weekly) had significantly decreased tumor weights after 3 weeks of therapy (p=0.002). Total metastatic events were also reduced in PG545 compared to gemcitabine and control treatment in the PanO2 model. Conclusion: PG545 inhibits tumor cell proliferation and migration in vitro and prolongs survival and inhibits tumor growth in vivo. Additionally it inhibits metastasis in vivo. Further studies are underway to elucidate the mechanism of inhibition and changes to pancreatic tumor microenvironment.

P11

Mechanisms of Resistance to Oncolytic Vesicular Stomatitis Virus in Malignant Melanoma A. Blackham,* S.A. Northrup, J.H. Stewart. *Wake Forest School of Medicine, Winston-Salem, NC.*

Introduction: Mutant M protein vesicular stomatitis virus (M51R-VSV) is a novel anti-cancer therapy that selectively targets a variety of malignancies; however some cell lines are relatively resistant to VSV. Herein we explore the mechanistic determinants of M51R-VSV sensitivity and resistance in malignant melanoma (MM) cells. Methods: Cell viability after M51R-VSV infection was measured by MTS assay in SK-Mel 3, SK-Mel 5, and SK-Mel 24 MM cells. Viral replication and protein synthesis were quantified by viral plaque assays and S 35-methionine electrophoresis, respectively. Interferon (IFN) responsiveness was evaluated by MTS assay after pre-treatment with β-IFN. Xenografts were established in athymic nude mice and treated with intratumoral M51R-VSV. Results: MM cells display varying degrees of M51R-VSV sensitivity. 48 hours after M51R-VSV infection (MOI 10 pfu/mL), SK-Mel 5, SK-Mel 3, and SK-Mel 24 cells demonstrated 0±2%, 57±6%, and 59±9% cell viability, respectively. Sensitive SK-Mel 5 cells support viral progeny and protein synthesis and when treated with β-IFN, became resistant to M51R-VSV (87±4% cell viability at 48 hours), indicating that IFN-mediated antiviral signaling is defective in these cells. Resistant SK-Mel 3 cells also support VSV infection and demonstrate IFN signaling defects, suggesting that other mechanisms, such as defects in apoptosis, confer resistance in SK-Mel 3 cells. In contrast, resistant SK-Mel 24 cells do not support viral infection but do possess intact apoptotic pathways induced by β-IFN. As an extension of our in vitro findings, treatment of SK-Mel 5 xenografts resulted in reduced tumor growth relative to controls after 26 days (-21±21% vs 2046±770%, p=0.015). M51R-VSV slowed but did not halt SK-Mel 3 tumor growth compared to controls (2013±810% vs 6955±2975%, p=0.11). Conclusions: Different mechanisms of VSV resistance exist in MM cells. While sensitive cells possess defects in antiviral signaling, resistant cells either have intact antiviral defenses or defective apoptotic signaling. Future work will focus on developing viral vectors to exploit specific resistant mechanisms to expand the therapeutic efficacy of M51R-VSV.



P12

SSEA-3 as a Novel Cancer Cell Cycle-Associated Marker

Y. Suzuki,* H. Takahashi, J. Nishimura, I. Takemasta, T. Mizushima, M. Ikeda, H. Yamamoto, M. Sekimoto, H. Ishii, Y. Doki, M. Mori. *Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.*

Human colorectal cancer (CRC) is a leading cause of cancer-related deaths in the Western world, and it is estimated to be one of the most frequently diagnosed cancers; estimated new cases of CRC were 146,970 and corresponding expected mortality was 49,920 in the United States in 2009 (National Cancer Institute website available at http://www.cancer.gov/cancertopics/types/colon-and-rectal). CRC is one of the most extensively investigated tumor types. Generally, a stepwise accumulation of genetic and epigenetic alterations in oncogenes and tumor suppressor genes is considered the driving force behind malignancies. Although recent models explain selected aspects of the complex process of CRC progression based on the hypothesis that many cancers are organized into hierarchies sustained by cancer stem cells (CSCs) at their apex and the concept generated excitement in many quarters of the clinical cancer research community, no crucial therapeutic target have been reported and defined because these markers express broadly in healthy tissues. Though it has been reported that pluripotency-associated stem cell markers have relation to the cancer stem cell-like properties, little is known about the relation between the dormancy and the stem cell surface markers. We found that stage-specific embryonic antigen (SSEA) –3, a glycolipid, which express during early stage of development, expressed at the invasive front of cancer in resected clinical colorectal cancer specimens. In HCT-116 cell line, fluorescence-activated cell sorter (FACS) - sorted SSEA-3(+) population showed faster growth in xenograft to NOD-SCID mice than SSEA-3(-) and unsorted population. Immunoblotting for whole cell lysate between these populations revealed that SSEA-3 (+) had lower p21 and p27 level, while cell cycle activators including cyclins had no difference. These observations indicate that SSEA-3 can be a novel cell cycle associated marker and a novel therapeutic target for colorectal cancer patients in addition to the conventional anti-proliferative regents.

P13

Higher Flow Rates Improve Heating during Hyperthermic Intraperitoneal Chemoperfusion M.J. Furman,* R.J. Picotte, M.J. Wante, B.R. Rajeshkumar, G.F. Whalen, L.A. Lambert. *University of Massachusetts Medical Center, Department of Surgical Oncology, Worcester, MA.*

Background: Heated intraperitoneal chemotherapy kills cancer cells through thermal injury and improved chemotherapeutic cytotoxicity. We hypothesize that higher flow rates during hyperthemic chemoperfusion (HIPEC) improve peritoneal heating and HIPEC efficacy. Methods: (1) A HIPEC model (30.8L capacity cooler attached to a Bio-Console 560 Medtronic extracorporeal pump) was filled with 26L of 37°C water containing a suspended 1L saline bag (SB) wrapped in a cooling sleeve to create a constant heat sink. (2) HIPECs were

performed in a Yorkshire swine model. Inflow, outflow, and peritoneal temperatures were monitored as flow rates were varied. (3) Flow rates and recorded temperatures during 20 clinical HIPECs were retrospectively reviewed. Results: In the HIPEC model, higher rates of flow decreased the time required to raise the temperature of the waterbath and SB to 43°C. With a constant heat sink, the minimum flow rate required to reach 43°C in the waterbath was 1.75L/min. Differences in temperature between the waterbath and SB were greatest at higher rates of flow (Table 1). In the swine model, the minimum flow rate required to reach 43°C outflow was 2.5-3.0L/min. Higher flow lead to more rapid heating of the peritoneum and greater temperature differences between the outflow and peritoneum. Review of 20 HIPEC procedures suggested that increased flow resulted in more rapid heating of the peritoneum. Conclusions: There is a minimum rate of flow required to reach goal temperature during HIPEC. Higher rates of flow raise intraperitoneal temperatures faster and may protect viscera through a greater temperature gradient. Flow rates should be maximized during HIPEC.

Table 1

Flow rate (L/min)	Time for WB to reach 43C (min)	Temperature difference between WB and SB when WB reached 43C without heat sink (degrees °C)	Time for WB to reach 43C with heat sink (min)
1	54	0.8 °C	NR
2	37	0.9 °C	70
3	29	1.4 °C	50
4	24	1.7 °C	37

→NR: (Not Reached) maximum temperature reached at 1L/min flow was 41.6C at 90 minutes after flow initiated

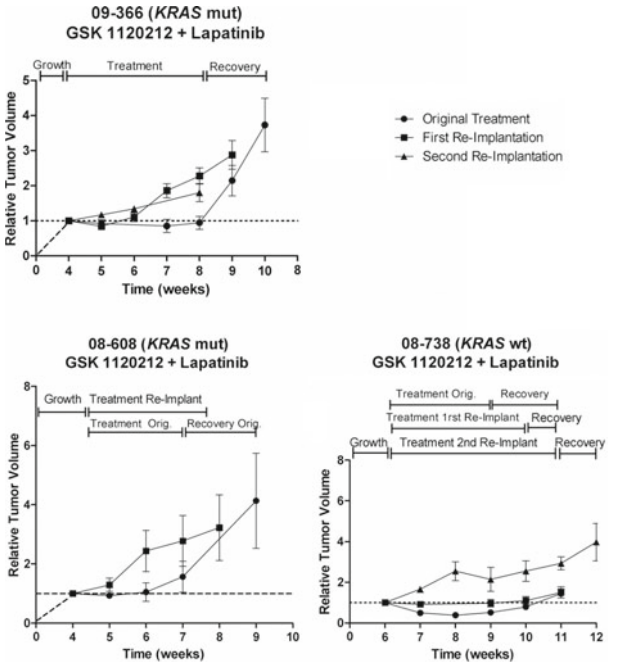


Figure 1: Response to treatment with lapatinib (65mg/kg, twice daily) and GSK1120212 (0.3mg/kg, daily). Following implantation, tumors were allowed to grow to ~100-500mm^3 prior to onset of treatment. Volume at treatment onset was used to calculate the change in relative tumor volume.

P14

Acquired Resistance to Combination Therapy with Lapatinib and MEK 1/2 Inhibitor GSK1120212 in an *in vivo* Murine Model of Pancreatic Cancer J.M. Lindberg,[1]* D.M. Walters,[1] S.J. Adair,[1] C.R. Cowan,[2] J.B. Stokes,[1] C.A. Borgman,[2] E.B. Stelow,[3] B.T. Lowrey,[1] M.E. Chopivsky,[1] J. Parsons,[2] T.W. Bauer.[1] *1. University of Virginia - Department of Surgery, Charlottesville, VA; 2. University of Virginia - Department of Microbiology, Charlottesville, VA; 3. University of Virginia - Department of Pathology, Charlottesville, VA.*

Purpose: Mutations of the oncogene *KRAS* and activation of cell-surface receptor tyrosine kinases are important and preserved mechanisms of tumorgenicity in pancreatic cancer. Dual inhibition of the downstream *KRAS* effector MEK 1/2 and tyrosine kinases EGFR and Her2 results in effective inhibition of patient-derived tumor growth in a murine orthotopic transplantation model. Because combinatorial therapies are moving rapidly into clinical trials, we sought to develop a model of acquired tumor resistance to this combination therapy. **Methods**: Patient-derived pancreatic tumor xenografts MAD 09-366 (*KRAS* mut), MAD 08-608 (*KRAS* mut) and MAD 08-738 (*KRAS* wt) were implanted orthotopically in nude mice and treated with combination lapatinib (EGFR/Her2 inhibitor) and GSK1120212 (MEK1/2 inhibitor). Tumor volume was measured by MRI. Following treatment, tumors were allowed to recover off therapy, then reimplanted in second and third generation mice and retreated. Drug-resistant and pre-treatment control tumors were evaluated by phospho-RTK and phospho-MAPKinase array. **Results**: Acquired resistance developed in all three tumor xenografts (Fig. 1). A comparison of pre-treatment mean tumor volumes demonstrated a significant decrease in tumor size from the original (F_0) to second re-implanted (F_2) generations suggesting selection for slower growing tumors. Phospho-RTK and phospho-MAPKinase array data demonstrated increased activation of FGFR1, VEGFR1/3, GSK-3β, p38, and Akt in resistant tumors as compared to their pre-treatment controls. These may represent mechanisms of tumor resistance and warrant further investigation. **Conclusion**: Repeated tumor exposure in vivo to combination treatment with GSK1120212 and lapatinib was used to develop a preclinical, orthotopic murine model of acquired drug resistance in patient-derived pancreatic cancers. This model provides the opportunity to define the mechanism of resistance in an appropriate tumor microenvironment and to develop alternative strategies for treating tumors resistant to this and other emerging therapies.

P15

Chemo Resistance of Pancreatic Cancer May be Reversed by Blocking the Pro-Survival AKT/P13K/mTOR and Mutant KRAS Signaling Pathways H.J. Wanebo,[1]* S. Lu,[2] C. Cong,[2] D. Shrayer,[3] Y. Wan,[4] W. Bowen.[2] *1. Surgical Oncology, Landmark Medical Center, Woonsocket, RI; 2. Brown University, Providence, RI; 3. Roger Williams Medical Center, Providence, RI; 4. Providence College, Providence, RI.*

Introduction: Pancreatic adenocarcinoma a highly lethal malignancy (5 yr survival 5%) is poorly responsive to chemotherapy. C6 Ceramide induces chemo enhancement of Gemcitabine(Gem),paclitaxel(Pax) and Cetuximab(Cetux). Exploration of the C6 mechanism suggests reversal of chemo resistance pathways–pro-survival and mutant KRAS in pancreatic cancer cells. Methods: In vivo: 2-3 month SCID male mice with pancreatic (pan) tumor implants (2 x 10-6 L3.6 cells) received intraperitoneal (I.P.) injections (3x/wk) of Pax (3.0mg/gm),Gem,10mg/gm) with/without C6 ceramide (10mg/ml) and were observed 6 weeks and tumor response/survival recorded. In vitro:The MTT anti tumor response to drugs Pax 3ug/ml,Gem 3ug/ml,C6 Ceramide10ug/ml was measured in 3 pancreatic lines L3.6, PANC-1,and MIA (Kras mutated). Signaling activation by Western blot utilized antibodies: LY294002, and Wortmannin to block PI3K/AKT pathway, U0126 and PD 98059 to block ERK pathway and Rapamycin to block mTORC1 pathway. Results: Combined therapy with C6 Ceramide induced significant inhibition of exponential tumor growth and prolonged survival by Gem and Pax. Administration of Gem or Pax with C6 Ceramide induced a significant increase in cell death and apoptosis in pancreatic cancer cells (L3.6, PANC-1 and MIA PaCa-2) which were associated with inhibition of cell signaling pathways including pro-survival PI3K/Akt/mTOR, and ERK/MAPK, KRas signaling pathways. Pharmacological inhibition with specific signaling pathway inhibitors enhanced cytotoxicity by Gem or Pax, suggesting that survival pathway inhibition might be the key mechanism contributing to C6 Ceramide synergism of Pax or Gem antitumor effects. We also showed C6 ceramide potentiation of Cetuximab anti tumor effects on Kras mutant MIA cells thus overcoming (EGFR mAb) resistance by inhibiting pro-survival PI3K/AKT/mTOR and bypassing mutant KRAS Ras-ERK pathways. Conclusion: C6 Ceramide an apoptosis signal potentiates the anti tumor effects of Gem, Pax and the EGFR Inhibitor Cetux against 3

aggressive pancreatic cancer cell lines by apparent inhibition of pro-survival PI3K/AKT/mTOR and Kras mutated pathways.

P16

Gadd45a Levels in Breast Cancer are Hormone Receptor Dependent A.I. Willis,* B. Powers, J.S. Tront, Y. Huang, B. Hoffman, D. Liebermann. *Surgery, Temple University School of Medicine, Philadelphia, PA.*

Introduction: Gadd45 alpha (a) is a member of the Gadd45 family of genes that are known stress sensors. Gadd45a has been shown to serve as an effector in oncogenic stress in breast carcinogenesis in murine models. The aim of this study was to analyze the impact of Gadd45a as a modulator in human breast cancer depending upon breast cancer receptor status. Methods: Breast tissue samples were obtained of female breast surgery cases from an academic institution's pathology repository. Slides were prepared by surgical pathology laboratory. Immunohistochemistry (IHC) was performed using Gadd45a antibody. Slides were prepared in triplicate and read by three readers, including an attending pathologist in cytology, for percent staining of cellular cytoplasm. Results: 38 female breast surgery cases were studied and grouped as: Normal (7, benign mammoplasty), Luminal A (8, ER+, PR+, HER2-; LumA), HER2+ (9, ER+, PR+, HER2+), and Triple Negative (14, ER-, PR-, HER2-; TN). There was a highly significant difference in percent Gadd45a staining between groups [Mean (± SE)]: Normal 17.4% (± 7.4); LumA 84.8% (± 2.4); HER2+ 59.0% (± 11.6); TN 25.4% (± 8.6), P<0.0001, ANOVA. Percent stained results for each specimen were averaged and categorized as: Negative (0-<10%, Neg), Low (10 - <40%), Medium (40 - <70%, Med), or High (≥70%). Gadd45a IHC levels for Normal cases found 86% Neg or Low. LumA breast cancer cases were found to be 100% High. Her2+ cases were 44% High, 33% Med, 22% Neg or Low. TN cases were 79% Neg or Low. This difference in distribution of Gadd45a levels across breast cancer receptor subtypes was significant, P=0.0008, Fisher's exact test. Conclusions: Gadd45a levels are highly significantly associated with hormone receptor status in human breast cancer. Normal breast tissue has low levels of Gadd45a. High Gadd45a levels are associated with LumA. HER2+ is associated with High and Med levels. Absence of hormone receptor in TN breast cancer is associated with Neg or Low levels of Gadd45a. Further studies are indicated to elucidate the role of Gadd45a in breast cancer as a potential tumor suppressor, prognosticator or target for treatment.

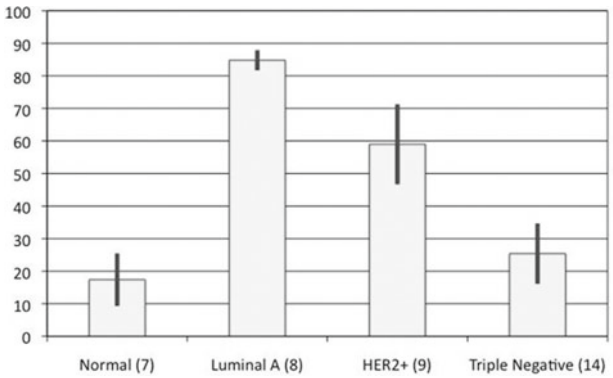


Figure 1: Percent Staining for Gadd45 alpha in human breast cancer

P17

WITHDRAWN

P18

Triptolide Induces Apoptosis in Pancreatic Cancer Cells through Down-regulation of Janus-Kinase 2 V. Dudeja,* G. Beyer, S. Banerjee, S.J. Skube, V. Sangwan, R.K. Dawra, S.M. Vickers, A.K. Saluja. *Surgery, University of Minnesota, Minnespolis, MN.*

Introduction: We have previously shown that triptolide, a natural compound, induces caspase dependent apoptotic cell death in pancreatic cancer. We have now modified triptolide to yield a water soluble drug Minnelide which markedly reduces the growth and loco-regional spread of pancreatic tumors in orthotopic animal models as well as human xenograft models of pancreatic cancer. Phase I clinical trials with Minnelide will start soon. The mechanism by which triptolide induces cell death is unclear. Janus Kinase-2 (JAK-2) is a pro-survival kinase which is up-regulated in a variety of cancers. In the current study we have evaluated the role of JAK-2 in triptolide induced apoptotic cell death in cancer. Methods: Pancreatic cancer cell lines were treated with triptolide and the effect on JAK-2 phosphorylation and the levels of the protein and mRNA of its downstream mediators c-myc, cyclin D-1, XIAP and survivin was evaluated. The role of JAK-2 in pancreatic cancer cell survival was evaluated by measuring the effect of JAK-2 inhibitors WP1066 or FLLL-31 on viability and apoptosis. To evaluate whether JAK-2 downregulation by triptolide sensitizes pancreatic cancer cells to other agents like TRAIL (agonist for recently discovered death receptors), the effect of TRAIL on viability and apoptosis parameters was measured with or without JAK-2 inhibition by triptolide or FLLL-31.Results: Triptolide inhibits the phosphorylation of JAK-2 and decreases the protein and mRNA levels of c-myc, cyclin D-1, XIAP and survivin thus suggesting that Triptolide downregulates JAK-2. Inhibition of JAK-2 by chemical inhibitors decreases viability and increases caspase-3/9 and annexin suggesting that silencing JAK-2 induces caspase dependent apoptosis. Furthermore, JAK-2 downregulation by triptolide or FLLL-31 (table) markedly sensitize pancreatic cancer cells to TRAIL induced cell death. Conclusion: Triptolide induces apoptotic cell death in pancreatic cancer cells through down-regulation of JAK-2 pathway. Its novel water soluble derivative Minnelide has immense potential to emerge as an effective therapy against pancreatic cancer, either alone or in combination with other agents like TRAIL.

JAK-2 inhibition markedly sensitizes pancreatic cancer cells to TRAIL induced cell death and apoptosis.

	S2-VP10				
	Viability (48h)	Annexin V (48h)	Caspase 3 (24h)	Caspase 8 (12h)	Caspase 9 (12h)
Control	100 ± 0	9 ± 2	100 ± 0	100 ± 0	100 ± 0
TRAIL 20ng/mL	114 ± 1	10 ± 1	150 ± 36	114 ± 12	109 ± 7
FLLL31 5μM	63 ± 22	13 ± 2	242 ± 2	129 ± 29	162 ± 1
FLLL31 5μM + TRAIL 20ng/mL	24 ± 11*	59 ± 11*	3890 ± 910*	842 ± 252*	295 ± 57*
	S2-013				
	Viability (48h)	Annexin V (48h)	Caspase 3 (24h)	Caspase 8 (12h)	Caspase 9 (12h)
Control	100 ± 0	14 ± 2	100 ± 0	100 ± 0	100 ± 0
TRAIL 20ng/mL	87 ± 5	16 ± 2	231 ± 74	143 ± 5	146 ± 11
FLLL31 5μM	47 ± 9	30 ± 1	357 ± 77	116 ± 7	111 ± 11
FLLL31 5μM + TRAIL 20ng/mL	21 ± 3*	92 ± 4*	3812 ± 546*	758 ± 380*	723 ± 448*

Data expressed as % of control (mean ±SEM) except for annexin where data reflects actual values of annexin positivity.
* p value <0.05 as compared to TRAIL alone.

P19

Tumor Irradiation Enhances the Efficacy of Adoptive T-cell Therapy: Effects on Host and Donor T-cells M. Egenti,* S. Wei, S. Teitz-Tennenbaum, A.E. Chang. *Surgery, University Of Michigan, Ann Arbor, MI.*

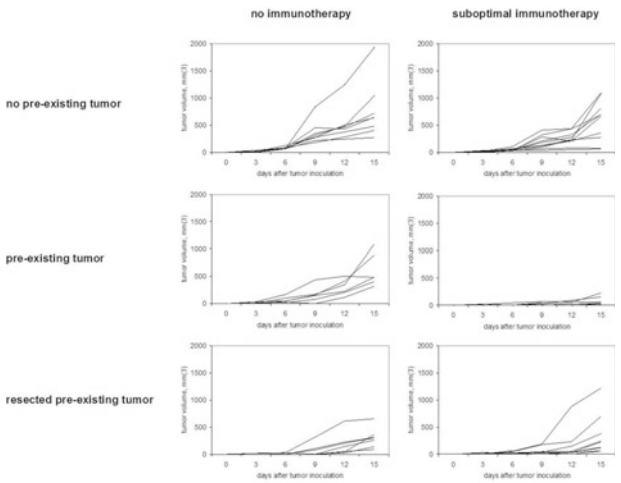
Purpose We wanted to study the effect of tumor irradiation on the therapeutic efficacy of adoptive T-cell therapy and the changes that occur in the host and the tumor micro-environment. Methods D5 melanoma tumor cells were subcutaneously injected into the flanks of C57BL/6 mice. On day 7post inoculation, the established tumors were irradiated for five consecutive days. On the last day of the irradiation, the mice were infused with tumor draining lymph node (TDLN) cells that had been activated and expanded in-vitro. The mice used to generated TDLN cells for transfer were congenic to the recipient mice in order to assess their function after transfer. Tumor growth and mice survival were monitored. Tumor, spleen and blood from recipient mice were collected for analysis of host and donor T-cell immune function. Results The effect of adoptive T-cell therapy (ACT) or tumor irradiation alone on tumor growth was minimal. However, the combination of tumor irradiation and ACT was significantly better than either alone in mediating tumor regression and conferred improved survival compared to all other groups. Tumor irradiation was associated with a significant increase in the proliferation of transferred T-cells when compared to host T-cells. This resulted in a significant increase of the ratio of donor: host T-cells in the tumor micro-environment. Furthermore, the percent of IFN-γ+ and TNF-α+ donor T-cells in the tumor micro-environment was increased after tumor irradiation. Tregs numbers were reduced

to a larger extent by local radiation in the systemic and tumor micro-environments. Using a standard T-cell proliferation assay, Tregs from mice subjected to tumor irradiation had impaired function. Conclusions Tumor irradiation enhanced the therapeutic efficacy of adoptive T-cell therapy. Mechanisms that may play a role in this synergistic effect appear to be in the increased proliferation of donor T-cells with an effector phenotype within the tumor microenvironment. In addition, tumor irradiation was associated with decreased Tregs in the tumor microenvironment which manifested impaired inhibitory function.

P20

Adoptive T-cell Immunotherapy Unmasks Concomitant Immunity: Novel Insight into the Influence of Tumor Burden on Cancer Immunotherapy A.J. Russ,[1]* S. Alam,[1] L. Wentworth,[2] J.V. Meyers,[1] S. Mahvi,[1] C.S. Cho.[1] *1. Section of Surgical Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI; 2. William S. Middleton Memorial VA Hospital, Madison, WI.*

Introduction. It has been speculated that adoptive immunotherapy using tumor-specific T cells would be best applied in settings of minimal disease burden. We have shown that tumors exert a global suppression of activation-induced T cell expansion. We have also found that the magnitude of this suppression is proportional to tumor burden, with large tumors exerting greater suppression than small tumors. We hypothesized that the efficacy of adoptive T cell immunotherapy would be impaired by the presence of large pre-existing tumors; moreover, we hypothesized that this impairment would be due to cancer-induced T cell suppression and not the presence of higher tumor antigen burden. Methods. B16F10 melanoma cells were stably transfected to express low levels of the viral peptide GP33 ("B16GP33"). C57BL/6 mice were inoculated with media, B16F10 tumors, or B16GP33 tumors on day 0 ("pre-existing tumors") and with contralateral B16GP33 tumors on day 9 ("index tumors"). On day 10, mice received media or 2x104 activated GP33-specific CD8+ T cells (a suboptimal dose for tumor control), and tumors were measured every three days. In some mice, pre-existing B16GP33 tumors were resected on day 6 prior to inoculation with index tumors. Results. In the absence of immunotherapy, growth of B16GP33 index tumors was unaffected by pre-existing B16F10 or B16GP33 tumors. As expected, suboptimal immunotherapy did not alter B16GP33 index tumor growth. Pre-existing B16F10 tumors did not alter the efficacy of immunotherapy; in contrast, the efficacy of immunotherapy was markedly enhanced in the presence of pre-existing B16GP33 tumors. This enhancement was lost when pre-existing B16GP33 tumors were resected prior to index tumor inoculation. Conclusions. Contrary to our hypothesis, larger tumor burden does not immunotherapy. Rather, immunotherapy appears to unmask concomitant immunity, in which growth of secondary tumors is suppressed by immune responses directed against large pre-existing tumors. This novel observation may help to define the clinical circumstances in which adoptive T cell immunotherapy should be utilized.



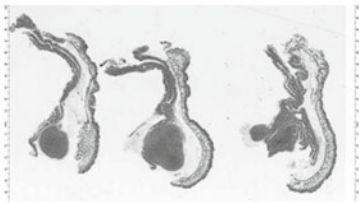
P21

Pilot Study for Efficacy of LEDC Ablation for Human Pancreatic Adenocarcinoma in a Murine Model C.R. St. Hill,* Y. Li, R.C. Martin II. *Surgery, Div of Surgical Oncology, University of Louisville, Louisville, KY.*

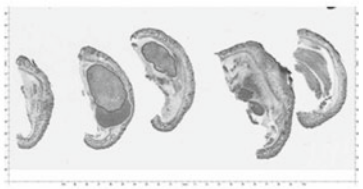
Purpose: Surgical resection remains the mainstay of treatment for pancreatic cancer however clinicians are challenged by patients with locally advanced, surgically unresectable disease. Current ablative technologies are limited by their inability to treat tumors near major vascular structures. Low Energy Direct Current (LEDC) ablation may offer an alternative in this regard. The primary purpose of this pilot study is to assess the feasibility of a human pancreatic adenocarcinoma xenograft in a murine model and to assess the efficacy of LEDC ablation for the local tumor destruction. Methods: A murine model was created by inoculating BALB/c nude mice with Panc-1 cells, human pancreatic adenocarcinoma cell line (ATCC:CRL 1469, Manassas, VA).Once the subcutaneous xenograft tumors reached adequate size LEDC ablation was performed under general anesthesia with muscle paralytic. Animal subjects were recovered and survived for 2, 7, 14, 21, 30, and 60 days prior to sacrifice and permanent fixation of tissues. Histologic evaluation assessed for viability. Results: A total of 39 male mice were used for the pilot study. The mean weight of the subjects remained stable throughout the study at 23.04g (SD 1.91). Body condition scores were recorded through the course of tumor growth and remained consistent at a mean value of 3/5 (SD 0.25) which is the goal for a healthy mouse. Representative tumor volume growth curves were plotted, the best fit line yielded the following linear equation: $y = 6.3082x - 53.352$ ($R2 = 0.6503$). Histologic data represented in figure 1. demonstrates the change in treated tumors over time. Early sacrificed tumors show small areas of non-viability surrounding the area of probe placement. As time progresses, mononuclear cells invest the tissue and the zone or percentage of non-viability increases. At more chronic time points the entire tumor appears non-viable with chronic inflammation and fibrosis replacing tumor. Conclusion: This pilot data demonstrates feasibility of a xenograft human pancreatic adenocarcinoma murine model and documents the histologic progression of tumor death over 60 days following LEDC ablation.

Figure 1.

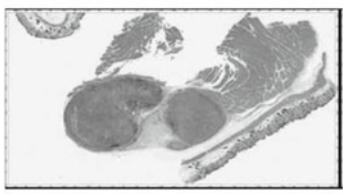
1A. Untreated control. Micrograph showing viable Panc-1 human tumor xenograft from untreated control.



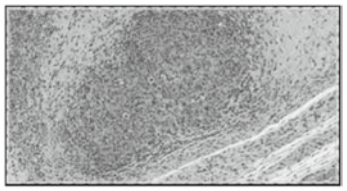
1B. 7 Day Post-Treatment Survival. Micrograph showing Panc-1 human tumor xenograft 7 days after IRE treatment. Using Aperio ScanScope xenograft is outlined with yellow. Non-viable tumor is outlined with red.



1C. 21 Day Post-Treatment Survival. No viable tumor present, tumor cells are surrounded by fibrosis, and mononuclear cells. There is viable muscle adjacent to tumor nodule.



1D. 21 Day Post-Treatment Survival. Shows tumor cells surrounded by chronic inflammation.



P22

A Complex Role for IL-17 in Melanoma Apoptosis and Proliferation M.B. Nicholl,* E.J. Herrick, Y. Fang. *Surgery, University of Missouri, Columbia, MO.*

IL-17, an inflammatory cytokine produced largely by TH17 T cells, is commonly found at sites of inflammation and cancer. Despite a controversial role in tumor growth in vivo, direct application of IL-17 to mouse melanoma cells in vitro has been shown to promote growth. The direct effects of IL-17 on human melanoma cells are unknown. This study was designed to discover the role of IL-17 in proliferation and apoptosis of a human melanoma cell line and investigate the molecular mechanisms governing the cytokine's effects. Clonogenic survival assay, immunohistochemistry (IHC), TUNEL staining, proliferation and caspase-3 activity kits were used to evaluate the effects of IL-17 on cell survival, proliferation and apoptosis. RT-PCR and IHC were used to investigate the underlying molecular mechanisms. Although TUNEL staining positivity and relative caspase-3 activity both increased after addition IL-17, the percentage of colonies, PCNA+ cells and the OD value of SK-Mel-5 cells also increased after addition of IL-17, suggesting the predominant role of IL-17 as pro-proliferation rather than pro-apoptosis. The pro-proliferative effect of IL-17 correlated with decreased expression of p27 and p53 and increased expression of cdk4. The pro-apoptotic effect of IL-17 correlated with decreased expression of Bcl-2 and survivin. This study provides further understanding of the direct effect of IL-17 on human melanoma cells. Further study is needed to understand how cellular proliferative mechanisms dominate apoptotic mechanisms despite an upregulation of pro-apoptotic factors.

P23

Apricoxib Enhances Response to Standard Therapy and Promotes Mesenchymal to Epithelial Transition in Pancreatic Cancer A.R. Kirane,* J.E. Toombs, K.T. Ostapoff, J.G. Carbon, R.E. Schwarz, R.A. Brekken. *UTSW, Dallas, TX.*

Current treatment for pancreatic cancer is minimally effective at prolonging survival, generating a need for novel strategies to augment standard therapy. Cyclo-oxygenase-2(COX-2) is expressed high levels in pancreatic cancer, is implicated in tumor progression and inhibition enhances cytotoxicity induced by gemcitabine or EGFR inhibition. The precise function of COX-2 in the tumor microenvironment is poorly understood, but is implicated in angiogenesis, apoptosis and epithelial to mesenchymal transition(EMT). Here, we investigate apricoxib, a novel COX-2 inhibitor in Phase II clinical trials, in combination with gemcitabine and erotlinib in pre-clinical models of pancreatic cancer. Baseline EGFR and COX-2 expression and functional response were determined in seven human pancreatic cancer cell lines. Cytotoxicity was determined for gemcitabine, erlotinib, and apricoxib independently and in combination, demonstrating notable increase in the activity of gemcitabine in combination with apricoxib. This effect was replicated in mice bearing orthotopic xenografts of AsPC-1, HPAF-II, and Colo357 cells. Tissue was analyzed by IHC & VEGF levels were determined by ELISA. Apricoxib was most effective at reducing growth and metastases in tumors with high COX-2 expression. VEGF levels correlated to degree of COX-2 expression and decreased in plasma in response to apricoxib, although tumor VEGF and microvessel density were unchanged. Regardless of COX-2 level, treatment with apricoxib resulted in vascular normalization. Furthermore, COX-2-inhibition decreased mesenchymal phenotype in comparison to control tumors, evidenced by decreased expression of Zeb1 and Vimentin and upregulation of E-Cadherin. Antiproliferative effect of apricoxib was only demonstrated in COX-2 dependent models. We conclude that apricoxib enhances the activity of gemcitabine and erlotinib in vitro and in vivo. While most potent effect is observed in high COX-2 expressing tumors, COX-2 negative tumors demonstrate improved response, likely from removal of the influence of stromal PGE2 production. These findings warrants further clinical evaluation in patients with pancreatic cancer.

P24

Identification and Characterization of Unique microRNA Expression in Colon Cancer Stem Cells N. Haraguchi,[1]* H. Ishii,[1] T. Satoh,[1] Y. Doki,[2] M. Mori.[2] *1. Department of Frontier Science for Cancer and Chemotherapy, Osaka University, Suita, Osaka, Japan; 2. Department of Gastroenterological Surgery, Osaka University, Suita, Osaka, Japan.*

Introduction: Cancer stem cells (CSCs) which have self-renewal and pluripotency capacity continuously supply the cancer cells. For these reasons, targeting of CSCs is thought to lead to the eradication of cancer cells. In colon cancer, CD133+, CD44+, CD166+ and ALDH+ cells have reported to express colon CSCs characters. To establish CSCs targeting therapy, we aimed to identify definitive colon CSCs marker and epigenetic regulator of colon CSCs which gives stem cell properties. Methods: Cell surface markers were analyzed after treatment of sodium butyrate (NaBT) which is well known to induce cellular differentiation. Expression of cell surface markers were confirmed in clinical colon cancer samples and limiting dilution assay was performed to assess tumorigenicity. Global analysis of microRNA and target scan was performed to identify CSCs regulators. Results: Expression of CD44 and CD49f was down regulated by NaBT treatment. Serial transplantation assay revealed that only CD44+CD49f+ formed tumor in immune-deficiency mice. By the Global analysis of microRNA, we have identified some sets of unique expression of microRNAs involved in iPS and ES cells in CD44+ CD49f+ cell fraction. Conclusion: CD44+CD49f+ cell fraction revealed colon CSCs characters. Some sets of microRNAs regulate colon CSCs and gives stemness properties.

P25

Cell Cycle Inhibition Enhances the Cytotoxicity of Hyperthermic Oxaliplatin M.J. Furman,* B.R. Rajeshkumar, G.F. Whalen, L.A. Lambert. *University of Massachusetts Medical Center, Department of Surgical Oncology, Worcester, MA.*

Background: The impact of cell cycle inhibition on cancer cell sensitivity to hyperthermic chemotherapy is unknown. This study investigates the effect of cell cycle inhibition by the cyclin-dependent kinase inhibitor, roscovitine, on the cancer cell-specific cytotoxicity of hyperthermic oxaliplatin. Methods: DLD colon cancer cells and MCF10A immortalized epithelial cells were treated with combinations of hyperthermia, roscovitine and oxaliplatin over a range of durations (30-120 minutes) and temperatures (37-43°C). Clonogenic assays and MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) were used to assess the impact of these treatments. Propridium iodide was used to quantify the cell cycle effects. Results: There was minimal toxicity from hyperthermia alone (43°C for 120 minutes) (Table 1). Roscovitine enhanced the sensitivity of DLD cells to hyperthermia at 43°C. There was a time (>90 min) and temperature (>40°C) dependent, cancer-specific, triple synergistic cytotoxicity between roscovitine, hyperthermia and oxaliplatin. Treating with roscovitine prior to hyperthemic oxaliplatin was more cytotoxic than the reverse sequence. There was greater cytotoxicity with the combined treatments in DLD than MCF10A. Roscovitine induced G2-cell cycle arrest in DLD and G1 arrest in MCF10A. Hyperthermia itself did not affect the cell cycle. Conclusions: This study demonstrates a cancer-specific synergistic cytotoxicity between the cell cycle inhibitor, roscovitine, hyperthermia and hyperthermic oxaliplatin. Clinical trials of roscovitine as an adjunct to hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis are warranted.

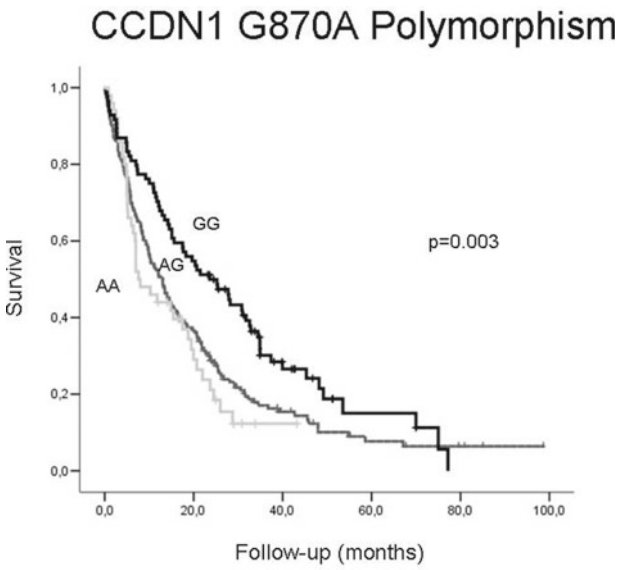
Table 1. Cancer-specific synergistic cytotoxicity bewteen roscovitine and hyperthermic oxaliplatin

Treatment	Cell Death (%)	
	DLD	MCF10A
Roscovitine (48 hrs)	36	0
Oxaliplatin (120 min, 40°C)	38	0
Oxaliplatin (90 min, 40°C) then Roscovitine (48 hrs)	64	3
Oxaliplatin (120 min, 40°C) then Roscovitine (48 hrs)	84	38
Roscovitine (48 hrs) then Oxaliplatin (90 min, 40°C)	74	43
Roscovitine (48 hrs) then Oxaliplatin (120 min, 40°C)	87	58

P26

Cyclin D1 is a Strong Prognostic Factor for Survival in Pancreatic Cancer: Analysis of CD G870A Polymorphismus and Immunohistochemistry K. Bachmann,* T. Rawnaq, A. Neumann, A. Hinsch, Y. Vashist, O. Mann, J. Izbicki, M. Bockhorn. *University Medical Center Hamburg Eppendorf, Hamburg, Germany.*

Introduction Cyclin D1 is an important regulator protein for the G1-S cell cycle phase transition and has impact on the regulation of proliferation and differentiation. It is known, that a deregulation of CD1 can lead to tumorgenesis. Therefore the aim of this trial was to evaluate the impact of the CCDN1 polymorphism G870A and corresponding protein expression and CCND1 amplification on the survival of the patients. Methods: 425 Patients with ductal pancreatic adenocarcinoma that underwent surgical resection (Partial pancreaticoduodenectomy) between 2001 and 2007 were included after histopathological confirmation. DNA was analyzed for CyclinD1 polymorphisms and immunhistochemical examination of the tumour was performed. Data were correlated with survival data by the Kaplan-Meier method followed by multivariate Cox regression analysis. Results: Overall 363 of 425 (85.4%) patients died during follow up; the mean survival was 22.9 months (20.5-25.3). The survival in patients with CD1 G870A polymorphism Adenine/Adenine was 15.1 months (95% CI 11.3-18.9), 21.5 months (17.4-25.6) for Adenine/Guanine and 29.4 months (95% CI 23.8-35.0) for Guanine/Guanine (p=0.003). A shorter survival was found for strong/moderate protein expression in IHC compared to weak/no expression (p=0.028). Additionally a significant coherency between unfavourable polymorphism (AA/AG) and increased protein expression was detected (p=0.005). Conclusions: A strong impact on survival of Cyclin D1 G870A polymorphism and the detected corresponding protein expression was found. The biological mechanism of CCDN1 in carcinogenesis has not been fully examined; this might be influenced by co-factors, that are still unknown, but at present CD1 seems to be an interesting biomarker for the prognosis of ductal adenocarcinoma of the pancreas.



P27

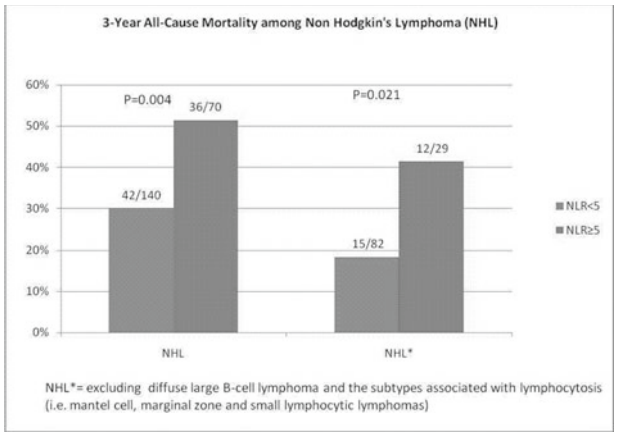
Epithelial-mesenchymal Transition Increases Tumor Sensitivity to COX-2 Inhibition A.R. Kirane,* J.E. Toombs, J.E. Larsen, K.T. Ostapoff, R.E. Schwarz, R.A. Brekken. *UTSW, Dallas, TX.*

Cyclooxygenase-2(COX-2) inhibitors, such as Phase II drug apricoxib, display antitumor activity but their mechanism of action lack clear definition. COX-2 inhibitors suppress VEGF production by tumor and stromal cells and display superior activity in vivo than in vitro, suggesting this class of drugs are antiangiogenic. We characterized the mechanism of action of apricoxib in HT29 colorectal and NSCLC cell lines to examine the effect of COX-2 inhibition on tumor functions. In vitro, the effect of apricoxib on proliferation and apoptosis was evaluated by comparing response of cells grown in monolayer culture to those forced to undergo epithelial to mesenchymal transition(EMT). Human tumor xenografts were grown in nude mice and apricoxib was given daily PO. Plasma drug and VEGF levels were quantified by LC-MS and ELISA, tumors were assessed for vessel density, apoptosis, proliferation and EMT immunohistochemistry. Apricoxib was weakly cytotoxic towards naive HT29 cells in vitro but inhibited tumor growth at well-tolerated doses. Pharmacokinetic analyses revealed that drug levels peaked at 2-4 μM and remained sufficient to completely inhibit PGE2 production but failed to reach concentrations cytotoxic for HT29 cells in monolayer culture. Despite this, tumor proliferation in vivo was almost completely abolished and apoptosis was induced in the absence of changes in microvessel density. However, drug treatment did increase pericyte coverage. Strikingly, apricoxib treatment induced a dose-dependent reversal of EMT, as shown by robust upregulation of E-cadherin and disappearance of vimentin and Zeb1 expression. Anchorage-independent growth conditions or forced EMT in vitro sensitized HT29 and NSCLC cells to apricoxib by 50-fold, suggesting occurrence of EMT may actually increase the dependence of cells on COX-2. We conclude that inhibition of COX-2 by apricoxib significantly inhibits tumor growth and progression by driving increased apoptosis, decreased proliferation, vascular normalization and a robust reversal of EMT. These data suggest that acquisition of mesenchymal characteristics sensitizes carcinoma cells to apricoxib resulting in significant single agent antitumor activity.

P28

Value of the Pretreatment Neutrophil to Lymphocyte Ratio in Predicting Long-term Mortality in Non-Hodgkin's Lymphoma Patients B. Azab,[1]* S. Arora,[1] N. Kohn,[2] M. Odaimi,[1] T. Terjanian,[1] A. Picon,[1] S. Bloom.[1] *1. Surgery, Staten Island University Hospital, Staten Island, NY; 2. Feinstein Institute for Medical Research, Manhasset, NY.*

Background : The neutrophil to lymphocyte ratio (NLR) at the time of cancer diagnosis is a strong independent predictor of mortality in different types of both solid and hematological malignancies, including diffuse large B-cell lymphoma (DLBCL). Recently in a large study including 8759 cancer patients, with blood counts collected within 2 years of the cancer diagnosis, NLR≥5 was an independent predictor of mortality in these patients. The prognostic value of NLR at the time of diagnosis in non-Hodgkin's lymphoma (NHL) subtypes other than DLBCL has not been studied yet. Therefore, the aim of our study was to determine whether the NLR is predictive of mortality in NHL other than DLBCL. Methods: A total of 210 patients had a differential leukocyte count recorded prior to chemotherapy treatment at the Hospital between January 2002 and December 2008. Survival status was retrieved from our cancer registry and social security death index. Survival analysis, stratified by NLR into two groups (NLR≥5 and NLR<5), was used to evaluate the predictive value of NLR in the 3.1 year follow-up period. We ran additional analysis excluding the DLBCL and NHL subtypes known to be associated with peripheral lymphocytosis (small lymphocytic, marginal zone and mantel cell lymphoma subtypes). Results: Of the 210 NHL patients, those with a pretreatment NLR ≥ 5 had a higher 3-year mortality (36/70=51% vs. 42/140=30%) compared to those with the NLR < 5 (p=0.004, according to two-tailed Fisher's exact test). After exclusion of the DLBCL and other subtypes associated with lymphocytosis, the patients with NLR ≥ 5 had a statistically significantly higher 3-year mortality (12/29=41% vs. 15/82=18%) than the patients with NLR<5 (p=0.0218). Conclusion: Our study demonstrated that NLR is not only a predictor of long-term mortality in patients with DLBCL but also in subtypes of NHL other than DLBCL.



The 3-year all-cause mortality among Non Hodgkin's Lymphoma patients according to their pretreatment Neutrophil/Lymphocyte ratio (NLR).

P29

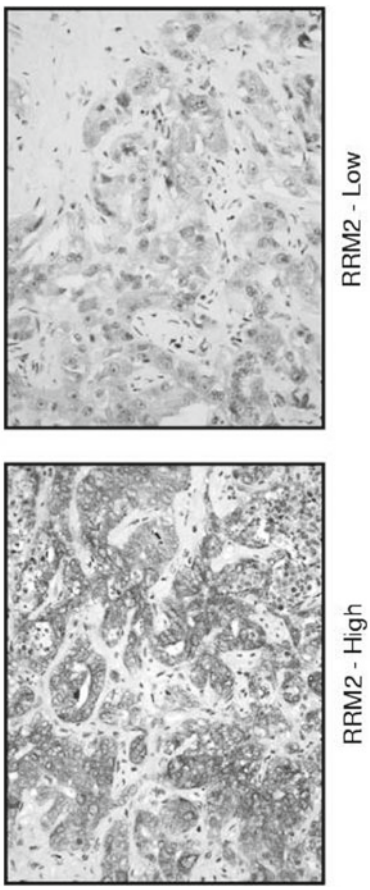
Somatostatin Receptor Subtypes 1-5 Gene Expression Differs in Multiple Sites in the Same Individual M. Hall,* T. Milosavljevic, P. Casey, C.T. Anthony, E.A. Woltering. *Department of General Surgery, Louisiana State University Health Sciences Center, New Orleans, LA.*

BACKGROUND: Metastatic tumors may be fundamentally different than the primary tumor. This phenomenon may partially explain resistance of metastatic disease to therapy. We evaluated the gene expression levels of somatostatin receptor subtypes 1-5 (SSTR 1-5) in patients with disseminated neuroendocrine tumors (NETS) undergoing cytoreduction of their primary tumor and its nodal and liver metastasis. METHODS: We compared the gene expression levels for SSTR 1-5 in primary tumor and their nodal and liver metastasis. The small bowel primary (SB), a mesenteric lymph node (LN) and a liver metastasis and their normal tissue counterparts were evaluated in four patients. RNA samples from each tissue underwent gene expression analysis using a customized Real Time Quantitative PCR (RT-qPCR) gene array. Normal tissue gene expression was compared to that obtained from the tumor sample at each site. RESULTS: SSTR 2 was overexpressed (four-fold or greater, $p \leq 0.01$) compared to control levels in 8/12 (67%) specimens; 4/4 (100%) of the liver specimens, 3/4 (75%) of the SB specimens, and 1/4 (25%) of the LN specimens. SSTR 2 gene overexpression was not observed in all three tumor sites in any patient. No tumor had SSTR 2 down-regulation. SSTR 5 was overexpressed (four-fold or greater, $p \leq 0.01$) compared to control levels in 6/12 (50%) specimens; 3/4 (75%) of the liver specimens, 2/4 (50%) of the SB specimens, and 1/4 (25%) of the LN specimens. SSTR 5 gene expression was up-regulated in all three tumor sites in one individual. SSTR 5 was down-regulated (7-fold, $p<0.01$) in one LN specimen. Changes in gene expression levels of SSTR 3 and SSTR 4 showed inconsistency between tumor sites, whereas that of SSTR1 was observed only at the metastatic sites. CONCLUSIONS: These results explain the observed variability in somatostatin receptor expression seen in 111In pentetreotide scans in multiple tumor sites from the same individual. The observation that gene expression varies from metastasis to metastasis may also help explain the difficulty in designing therapies that cure patients rather than inducing partial remissions.

P30

An Analysis of ERCC1, hENT1, RRM1, and RRM2 Expression in Intrahepatic vs Extrahepatic Biliary Tract Malignancy: Implications for Treatment? S.B. Fisher,[1] K.E. Fisher,[2] S.H. Patel,[1] B.F. El-Rayes,[3] C.A. Staley,[1] D.A. Kooby,[1] N. Adsay,[2] A.B. Farris,[2] S.K. Maithel.[1]* *1. Emory University, Division of Surgical Oncology, Atlanta, GA; 2. Emory University, Dept of Pathology, Atlanta, GA; 3. Emory University, Dept of Hematology-Oncology, Atlanta, GA.*

Background High tumoral ERCC1 expression is associated with reduced platinum chemotherapy efficacy, and we recently reported its association with decreased survival for patients with pancreas adenocarcinoma. Gemcitabine efficacy is related to tumor expression of hENT1, RRM1, and RRM2. The differential expression of these biomarkers in biliary tract malignancy (BTM) is not known. Methods 62 patients in whom tissue was available for analysis were selected from a prospective database of all patients (n=104) who underwent resection of a BTM between 1/00-12/08. Tumors were grouped as intrahepatic cholangioca (IC) or extrahepatic (EH: hilar, distal, and gallbladder cancer). Immunohistochemistry for ERCC1, hENT1, RRM1, and RRM2 expression was graded by a single pathologist. Results Median age was 67 yrs. Mean F/U was 31mo. Median tumor size was 3.5cm, 19% had a positive resection margin, and 37% had positive lymph nodes. Contrary to our previous finding that 16% of pancreas adenoca had high ERCC1 expression, only 3 BTMs (4%) had high ERCC1 expression. 92% and 81% of BTMs exhibited high hENT1 and RRM1 expression, respectively. Among these 3 biomarkers, there was no difference in expression patterns between IC and EH tumors. BTM exhibited variable RRM2 expression as 32% had high and 68% had low expression (Figure). RRM2 expression was different based on tumor location. The majority (60%) of IC exhibited high RRM2 expression compared to a minority (23%) of the EH tumors ($p=0.02$). High RRM2 expression in IC was associated with a trend towards reduced survival (29 vs 35 mo) while the opposite trend was observed for EH tumors (38 vs 24 mo). Conclusion ERCC1 expression is different for biliary tract malignancy (BTM) compared to pancreas adenoca. Most BTM demonstrate low ERCC1 expression and high hENT1 and RRM1 expression. RRM2 expression is variable and dependent on location of tumor, as intrahepatic cholangioca has the opposite expression profile of extrahepatic tumors. This finding may have implications for selection of chemotherapy agents (gemcitabine vs platinum) and interpretation of trials assessing chemotherapeutic efficacy.



RRM2 Expression: Low (top) vs High (bottom)

P31

Paradoxical Cross-Talk between the Stat3 and MAPK Pathways in CCL25-CCR9 Mediated Pancreatic Cancer Growth and Proliferation M. Le,* X. Shen, W. Lee, M. Duldulao, J. Garcia-Aguilar, J. Kim. *General and Oncologic Surgery, City of Hope Medical Center, Duarte, CA.*

Background: Chemokine receptors have been shown to regulate the progression of several malignancies. Signal transducer and activator of transcription 3 (Stat3) may contribute to the invasive phenotype of several human cancers, but its upstream signals have not been well characterized. Our objective was to investigate the relationship between the CCL25-CCR9 axis and Stat3 signaling in pancreatic cancer cells. Methods: We exposed two established human pancreatic cancer cell lines PANC-1 and MIAPaCa-2 to the cytokine CCL25 (800 ug/uL for 20 min) and measured the activation of Stat3 (phosho-Stat3) by Western blot assay. Stattic, a small molecule Stat3 inhibitor, was used (20uM) to antagonize Stat3 signaling. We also measured activation level of extracellular signal-regulated kinase (phospho-ERK) following CCL25 exposure and used UO126 (10uM), a small molecule MEK inhibitor, to antagonize the MAPK pathway. Changes in cell proliferation were measured by CellTiter Glo Fluorescence assay. Results: Constitutive phosphorylation of Stat3 was observed in both pancreatic cancer cell lines. Exposure of MIAPaCa-2 to CCL25 further increased phospho-Stat3 levels on Western blot assay. We also observed a concomitant increase in phospho-ERK levels with exposure to CCL25 in both cell lines. Exposure of pancreatic cancer cells to CCL25 significantly increased cell proliferation. To determine the mechanism of CCR9-mediated cell proliferation, we used stattic and UO126 to specifically inhibit Stat3 and MEK activation, respectively. Interestingly, pre-treatment with stattic prior to CCL25 exposure resulted in a paradoxical enhancement of phospho-ERK levels. Conversely, inhibition of the MAPK pathway with UO126 led to a paradoxical enhancement of phospho-Stat3 levels. Conclusions: Our results demonstrate that CCL25 activates Stat3 and MAPK pathways to contribute to pancreatic cancer proliferation. We also show potential cross-talk between Stat3 and MAPK pathways, wherein antagonism of one pathway resulted in paradoxical activation of the other pathway. Our findings suggest that therapeutic targeting of downstream pathways may require a multi-drug approach.

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Triptolide as a Novel Chemotherapeutic Agent for Treatment of Hepatocellular Carcinoma T.C. Krosch,* V. Sangwan, S. Banerjee, A.K. Saluja, E.H. Jensen, S.M. Vickers. *Department of Surgery, University of Minnesota, Minneapolis, MN.*

Background: Hepatocellular carcinoma is the most common malignant primary liver tumor worldwide, and systemic treatments are limited. Our lab has investigated triptolide as a potential chemotherapeutic option. This study evaluates the response of HuH-7 and Hep3B hepatocellular carcinoma cells to triptolide treatment. Methods: HuH-7 and Hep3B hepatocellular carcinoma cell lines were treated with triptolide and assessed for changes in viability (MTT assay), caspase activation (Promega), and Annexin V positivity (Guava Nexin). Real-time PCR was utilized to determine the changes in mRNA levels, and Western blots were used to determine expression of protein levels. Results: Triptolide treatment, administered in vitro at varying concentrations, demonstrated dose- and time-dependent cell death in both cell lines tested. Cell death occurred within 72 hours at a 100 nM concentration, with 80% death in Hep3B, but was less pronounced in HuH-7 (60% death). Cell death was accompanied by increased caspase-3 activation and Annexin V positivity in both cell lines, suggesting apoptosis. Previously published literature shows HSP70 and HSP27 to be upregulated proteins in metastatic hepatocellular carcinoma. Evaluation of mRNA levels showed levels of HSF-1, the transcription factor for HSP70 and HSP27, significantly decreased with triptolide treatment in both cell lines. Downstream expression of HSP70 and HSP27 was also significantly decreased. Consistent with these findings, protein expression of these proteins was markedly decreased at 72h time points, in comparison to untreated controls. Conclusions: Triptolide treatment of hepatocellular carcinoma cells in vitro induces cell death by apoptosis. Treatment results in decreased expression HSP70 and HSP27, two proteins found to be normally upregulated in metastatic disease. Our study suggests triptolide may serve as a therapeutic option in treatment of hepatocellular carcinoma.

P33

Genome Wide Analysis of Methylation in Well Differentiated and Dedifferentiated Liposarcomas A.A. Guzzetta,[1]* R.B. Kwak,[1] L. Danilova,[2] T. Fu,[1] E.P. Pappou,[1] J. Jeschke,[1] E.A. Montgomery,[2] N. Ahuja.[1] *1. Surgery, Johns Hopkins University, Baltimore, MD; 2. Johns Hopkins University, Baltimore, MD.*

Introduction: Epigenetic changes such as DNA methylation are commonly seen in human cancers and associated with transcriptional silencing of tumor suppressor genes such as p16. However, little is known of the epigenetic regulation of well differentiated (WDLPS) or dedifferentiated liposarcoma (DDLPS). We have used a genome wide approach to better understand DNA methylation changes and identify potential biomarkers. Methods: DNA was extracted from 3 liposarcoma cell lines, 2 primary tumors and 2 normal adipose tissues and submitted for Infinium Human Methylation 450K methylation assay. The data mining site Oncomine™ was used to compose a list of top 1% underexpressed genes in DDLPS. Methylated and underexpressed genes were chosen and tested via Methylation Sensitive Polymerase chain reaction (MSP) in the original cell lines and then validated in patient samples. Results: Methylation of all probes located within CpG islands and near a transcription start site was interrogated as a β value (β=0: 0% methylation; β= 1: 100% methylation). The mean β values for transcription start site probes were 0.096 in liposarcoma versus 0.093 in normal tissues demonstrating the low level of methylation in these tumors (p=0.00061). Probes that showed differential methylation between normal and cancer (β difference >0.14) were compared to the top 1% under-expressed genes in Oncomine. Only 14 novel genes met these criteria. 6 of these genes were then validated in cell lines. Two genes, FABP5 and AKR7A3, were confirmed to be methylated in cell lines but not in normal samples by MSP. 25 samples were obtained from 12 patients, including 8 WDLPS (grade 1); 15 DDLPS (grade 2-3) and surrounding normals. Nine tumors were primary and 13 tumors were recurrent. DNA methylation was an infrequent event with FABP5 methylation seen in one recurrent grade 3 DDLPS (5%). AKR7A3 methylation was seen in one recurrent grade 2 DDLPS and one recurrent grade 3 DDLPS (9%). Conclusion: Methylation-associated silencing of genes appears to be a rare event but may identify prognostic biomarkers. Further studies are needed to understand additional epigenetic regulatory mechanisms in sarcomas.

P34

Reduced Re-excisions while Conserving Tissue Volume Resected in DCIS Patients S.K. Boolbol,[1]* B.C. Freedman,[1] C. Cocilovo,[2] L. Tafra.[3] *1. Beth Israel Medical Center, New York, NY; 2. Inova Breast Center, Fairfax, VA; 3. Anne Arundel Medical Center, Annapolis, MD.*

Background The ability to obtain negative margins with a single surgical procedure remains a challenge, particularly in patients with Ductal Carcinoma in Situ (DCIS). Several techniques have been reported to lower the positive margin rate, at a cost of significant additional tissue resected. A novel device (MarginProbe®, Dune Medical Devices, Inc.) is intended to provide surgeons with real time, intraoperative detection of cancerous tissues at the margins of excised specimens. An analysis was performed to determine the impact on tissue volume of the previously reported improvement in candidates for re-excision associated with device use for patients with a DCIS component. Methods 596 patients who were undergoing breast conservation using needle localization were randomized in a prospective, international, multicenter (n=21) IRB approved study. Randomization occurred in the operating room, following standard of care lumpectomy, including palpation followed by indicated additional cavity resections. Device positive readings required additional resections of the cavity; device was used on main lumpectomy specimen only. Pathologists were blinded to study arm. Tissue volume of all specimens and resections was recorded. Since reducing candidates for re-excision requires removing additional tissue associated with cancer in the primary lumpectomy, we looked at total tissue volume removed across all surgeries, to assess the final impact to the patient. Results Results are presented in Table 1. Total tissue volumes removed during all surgeries (lumpectomy and re-excision procedures) was similar, while the decrease in candidates for re-excision was significant for all pathology involving DCIS. Candidates for re-excision excludes positive margins (<1mm) at skin or fascia. Conclusions Unlike other techniques for reducing re-excisions, device use does not require an increase in tissue

volume to achieve a significant reduction in the number of candidates for re-excision.

Table 1

Diagnosis	Group	Patients	Total tissue volume	Candidates for re-excision	p-value
		N	(cc)	%(N)	
DCIS	Device	83	83	13% (11/33)	p = 0.0004
	Control	78	76	37% (29/78)	
DCIS + invasive	Device	155	94	17% (26/155)	p < 0.0001
	Control	179	90	33% (59/179)	

P35

Are the American Society for Radiation Oncology (ASTRO) Guidelines Accurate Predictors of Recurrence in Early Stage Breast Cancer Patients Treated with Accelerated Partial Breast Irradiation?
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Background. The American Society for Radiation Oncology (ASTRO) consensus statement (CS) provides guidelines for pt selection for accelerated partial breast irradiation (APBI) following breast conserving surgery (BCS). The purpose of this study was to evaluate recurrence rates based on ASTRO CS groupings. **Methods.** A single-institution IRB-approved retrospective study was conducted from April 2004 to July 2010. We identified 238 pts with 243 breast cancers. All pts underwent BCS followed by APBI via balloon catheter brachytherapy. Pts were classified as "suitable", "cautionary" or "unsuitable" based on ASTRO CS guidelines. Rates of recurrence at each site were assessed. Balloon brachytherapy complication rates were also evaluated. **Results.** Of the 243 cancers, 23.1% were "suitable", 51.0% were "cautionary" and 25.9% were "unsuitable". Median follow-up was 3.2 yrs. There were 8(3.2%) ipsilateral breast tumor recurrences (IBTR) at a median of 3.1 yrs. The 4-yr actuarial IBTR rate was 5.1%. There were no significant differences in the 4-yr actuarial IBTR rates between the "suitable", "cautionary" and "unsuitable" categories (3%, 5.9% and 4.4%, respectively; p=0.79). The 4 yr-rate of IBTR was also not different between pts with ductal carcinoma in situ and invasive carcinoma (4.1% vs 5.5%, p=0.59). On univariate analysis, estrogen receptor negative invasive cancers trended towards a higher rate of IBTR (HR=5.59, p=0.06). There were 5(2.1%) regional recurrences and 4(1.7%) distant recurrences for the entire cohort. The rates of symptomatic seroma were 15.6%. Thirty(12.6%) pts developed a post-treatment infection, of which 5(2.1%) required incision and drainage. **Conclusions.** Early stage breast cancer pts treated with APBI had a low rate of IBTR with an acceptable complication rate. Recurrence rates were not significantly different based on ASTRO CS groupings. The ASTRO groupings are poor predictors of patient outcomes. Further studies evaluating individual clinicopathologic features are needed to determine the safety of APBI in higher risk pts.

Table 1. Patterns of tumor recurrence in 243 breast cancers treated with accelerated partial breast irradiation

Case no.	Age (yrs)	Criteria	ASTRO grouping	Local failure	Nodal failure	Distant failure
11	56	Tumor size > 3.0 cm, ER-negative, age 50-59	Unsuitable	No	No	Yes
22	78	ER-negative, close margin	Cautionary	Yes	No	No
25	70	Close margin, focal LVI	Cautionary	No	Yes	Yes
40.1	62	Positive margin, extensive LVI, ER-negative	Unsuitable	No	Yes	No
44	69	ER-negative	Cautionary	Yes	No	No
50	50	Age 50-59, DCIS ≤ 3 cm	Cautionary	Yes	No	No
55	50	ER-negative, age 50-59	Cautionary	No	Yes	No
71	45	Age < 50, close margin	Unsuitable	Yes	Yes	Yes
91.1	74	ER-negative, close margin	Cautionary	Yes	No	No
107	66	Positive margin, multifocal 2.1-3.0 cm	Unsuitable	Yes	Yes	No
131	52	Positive margin, ILC, tumor size 2.1-3.0 cm	Unsuitable	No	No	Yes
147[a]	80	N/A	Suitable	Yes	No	No
208	59	Close margin, age 50-59, DCIS ≤ 3 cm	Cautionary	Yes	No	No

ER estrogen receptor, *LVI* lymphovascular invasion, *DCIS* ductal carcinoma in situ, *ILC* invasive lobular carcinoma

[a] This patient had a mixed ILC/IDC tumor.

P36

Post-treatment Surveillance for Breast Cancer Patients: What Motivates the Experts?
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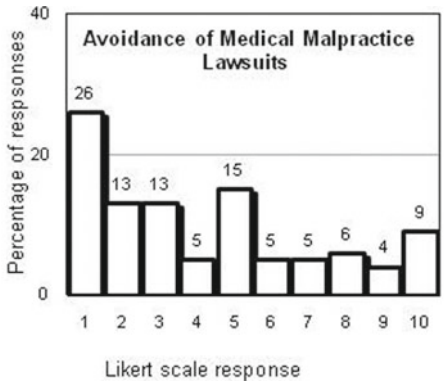
Introduction: Breast cancer is the most common cancer among American women, except for skin cancer. The chance of developing invasive breast cancer at some time in a woman's life is about 12%. As survival rates have increased, more women are eligible for post-treatment surveillance. Because post-treatment surveillance is commonly done after initial cancer therapy, and because there is a wide variation in surveillance strategies employed by clinicians, we sought to determine what factors motivate physicians who carry out surveillance after primary treatment of breast cancer. Methods: A custom-designed survey instrument with eleven questions about potential motivating factors was e-mailed to the 3245 members of the American Society of Clinical Oncology (ASCO) who had identified themselves as having breast cancer as a major focus of their practice. Responses were submitted on a 10-level Likert-type scale (1 least important and 10 most important). The percentage of responses for each point on the scale for each of the 11 potential motivating factors was calculated. Ranking was done according to the strongest factor (percentage with score of 10) and weakest factor (percentage with score of 1). Results: There were 1013 responses (31%) submitted. Of these, 734 (73%) were evaluable and included in our analysis. Potential detection of a second primary breast cancer was the strongest motivating factor (53% of responses with a score of 10). The weakest potential motivating factor was avoidance of medical malpractice lawsuits (26% of responses with a score of 1). Conclusions: 1) Despite evidence based guidelines, surveillance practice patterns vary widely. 2) Many potential factors appear to motivate clinicians. 3) To our knowledge, this is the first report of such motivating factors. 4) Our data could help understand why variation exists and thereby devise strategies to minimize it.



Weakest Motivating Factor

P37

The Rise and Fall of Breast Conservation Surgery in Early-stage Breast Cancer
C.A. Kotwall,[2]* M.N. Merritt,[1] A. Adams,[1] N. Kilbourne.[1] *1. Surgery, New Hanover Regional Medical Center, Wilmington, NC; 2. University of North Carolina-Chapel Hill, Chapel Hill, NC.*

Introduction: Twenty years ago, the National Institutes of Health stated that breast conservation surgery (BCS) was appropriate for Stage I and II breast cancer, and subsequent randomized trials have documented survival equivalence. However, recent studies continue to show underutilization of BCS. We sought to review our prevalence of BCS, and also to identify patient and tumor characteristics associated with the use of BCS in early-stage breast cancer. Methods: We retrospectively reviewed our breast cancer data base from 1990 to 2010 and identified 3280 women with ductal cancer in situ and early-stage invasive breast cancer (size < 4cm; N0, N1) at one institution. Multiple logistic regression (MLR) was used to determine various patient and tumor factors associated with BCS. Results: Our prevalence of BCS was 18% in 1990, then rose to a high of 45% in 1999, and then fell to 28% in 2010 for tumors < 4cm. When recalculated for tumors < 3cm,

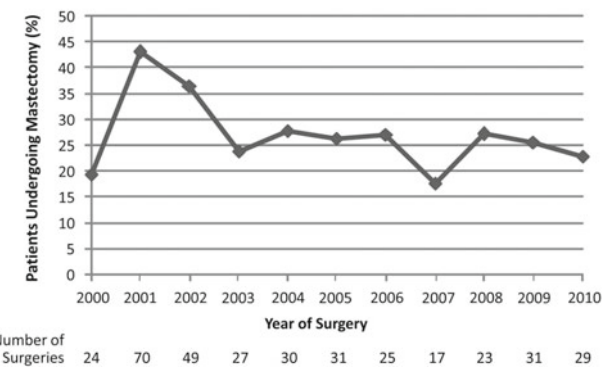
the prevalence of BCS was 20, 48, and 29%, for the same time periods. Variables examined were age, ethnicity, payer source, tumor size, tumor grade, estrogen receptor status, S-phase fraction (SPF), nodal status, stage, and year of diagnosis. In univariate analysis, significant variables associated with the use of BCS were African-American versus Caucasian women (p=0.006), smaller tumor size in 10 mm increments from < 10 to 39mm (p<0.0001), decreasing stage from Stage II down to Stage 0 (p<0.0001), and low versus high SPF (p=0.006). In the MLR model, only smaller tumor size (p<0.0001), decreasing tumor stage (p=0.004) and self-pay status (p=0.017) were more likely to be associated with BCS. Conclusion: In this large series of women with early-stage breast cancer, we had initially shown a rise in the prevalence of BCS that has now fallen over the last 10 years. BCS is used more often in women with small tumor size, Stage 0 and I breast cancer, and in those who are self-pay. More effort should be directed at counseling women with early-stage breast cancer regarding the merit of breast conservation surgery.

P38

Effect of Pre-operative MRI on Mastectomy and Contralateral Prophylactic Mastectomy Rates at a Community Hospital by a Single Surgeon C. Guilfoyle,[1]* M.K. Christoudias,[1] A.E. Collett,[1] E.J. Gracely,[2] T.G. Frazier,[1] A.V. Barrio.[1] *1. Department of Surgery, The Bryn Mawr Hospital, Bryn Mawr, PA; 2. School of Public Health, Drexel University College of Medicine & Drexel University, Philadelphia, PA.*

Introduction: The use of magnetic resonance imaging (MRI) in the pre-operative evaluation of newly diagnosed breast cancer (BC) patients has been associated with higher mastectomy and contralateral prophylactic mastectomy (CPM) rates. We evaluated the effect of pre-operative MRI as a function of surgical year with respect to mastectomy and contralateral prophylactic mastectomy (CPM) rates by a single surgeon. Methods: From January 2000 to December 2010, 1,279 newly diagnosed surgically treated breast cancer patients with 1,296 cancers were identified. Our current breast MRI was installed in the Comprehensive Breast Center in April 2006. Mastectomy and CPM rates were evaluated by surgical year and further stratified as "pre-MRI" or "post-MRI" depending on whether surgery occurred prior to or after April 2006. Results: Of 1,296 cancers, 923 (71.2%) were treated with breast conserving surgery (BCS) and 373 (28.7%) with mastectomy. There was a significant increase in the percentage of patients undergoing MRI in the "pre-MRI" vs. "post-MRI" era (17.2% vs. 78.7%, p <0.001), with a steady increase first noted in 2004. In contrast, mastectomy rates decreased over time with 29.9% undergoing mastectomy before 2006 vs. 24.5% after 2006 (p = 0.038). Except for 2007, where there was a drop in CPM rates to 7.1%, CPM rates increased over time from 16.7% in 2000 to 51.9% in 2010 (p = 0.033). Conclusions: In our community hospital, mastectomy rates have decreased over time despite the increased use of pre-operative MRI. MRI alone may not explain the increasing rates of mastectomy reported in other series. Conversely, CPM rates have dramatically increased over time. Further studies are needed to assess the role of surgeon bias, along with other factors, in surgical decision making.

Figure 1. Percentage of patients undergoing mastectomy by surgical year



P39

The Impact of Breast Reconstruction on the Decision to Undergo Contralateral Prophylactic Mastectomy L.J. McGhan,[1]* B.A. Pockaj,[1] R.J. Gray,[1] S.P. Bagaria,[2] S.A. McLaughlin,[2] W.J. Casey, III,[1] A.M. Rebecca,[1] N. Wasif.[1] *1. Mayo Clinic in Arizona, Phoenix, AZ; 2. Mayo Clinic in Jacksonville, Jacksonville, FL.*

Background: In the last decade there has been an increase in the use of contralateral prophylactic mastectomy (CPM) in patients with unilateral breast cancer and DCIS undergoing mastectomy. Although many factors have been proposed to explain this trend, the impact of breast reconstruction on the use of CPM has not been extensively studied. Methods: A retrospective review of patients with unilateral invasive breast cancer or DCIS from Surveillance, Epidemiology and End Results (SEER) registry data (2004-2008) was conducted. Characteristics of patients undergoing CPM were evaluated. Results: 102,674 patients diagnosed with DCIS or stage I-III infiltrating breast cancer underwent mastectomy for their primary lesion. Of these, 16,197 patients (16%) underwent a CPM. A significantly higher proportion of women undergoing CPM had reconstruction performed (36%) than those patients not undergoing CPM (11%), p<0.001. On multivariate analysis, significant variables predicting CPM included younger age (especially <45 yrs, with significantly decreased odds ratio (OR) with advancing age group), breast reconstruction, lobular histology, stage I disease, and advancing year of surgery (2008 vs. 2004) (all p<0.001); Table. Of the 20,760 patients (20%) who underwent reconstruction, 7410 (36%) had implant reconstruction, 7705 (37%) had tissue reconstruction, and 1941 (9%) had combined tissue/implant reconstruction (no data for 18%). On multivariate analysis, predictors of reconstruction included young age (OR for age groups <45, 46-60, 61-80 and >80 yrs: 1.00, 0.68 (CI 0.65-0.71), 0.19 (CI 0.18-0.20) and 0.02 (CI 0.015-0.023), respectively), year of surgery (2008 vs. 2004: OR 1.40; CI 1.33-1.48), lobular histology (OR 1.26; CI 1.22-1.31), CPM (OR 3.08; CI 2.96-3.20) and no radiation performed (OR 1.23; CI 1.17-1.30). Conclusions: Besides age, undergoing reconstructive surgery is the factor most strongly associated with CPM. This suggests that apart from risk reduction, the availability of and/or patient willingness to undergo breast reconstruction influences the decision to undergo CPM.

		Odds Ratio^	95% CI
Age (yrs)	<45	1.00*	
	46-60	0.60	0.58-0.63
	61-80	0.30	0.28-0.32
	>80	0.09	0.08-0.11
Race	Caucasian	1.00*	
	Black	0.46	0.44-0.50
Malignant Behavior	Invasive cancer	1.00*	
	DCIS	2.56	0.20-33.7
Histology	IDC	1.00*	
	ILC	1.41	1.33-1.51
Tumor Stage	III	1.00*	
	0	3.70	0.28-48.6
	I	1.44	1.35-1.55
	II	1.18	1.13-1.26
Year of Surgery	2004	1.00*	
	2005	1.13	1.06-1.21
	2006	1.33	1.25-1.42
	2007	1.72	1.61-1.82
	2008	1.92	1.81-2.03
Reconstruction	No	1.00*	
	Yes	3.58	3.41-3.75
Radiation Therapy	No	1.00*	
	Yes	0.99	0.93-1.04

Table: Predictors of CPM (all p<0.001); *Referent

P40

Can Sentinel Node Biopsy before Preoperative Chemotherapy Predict Patients Who Do Not Need Axillary Dissection? J. Kawano,[1]* N. Hayashi,[1] S. Ohde,[1] A. Yoshida,[1] E. Nakano,[1] K. Tsugawa,[2] S. Nakamura,[3] H. Yagata,[1] H. Yamauchi.[1] *1. St. Luke's International Hospital, Tokyo, Japan; 2. St. Marianna University school of Medicine, Kanagawa, Japan; 3. Showa University, Tokyo, Japan.*

Positive sentinel node (SN) predicts the presence of non-sentinel node (nonSN) metastases in primary breast cancer patients. Our purpose is to estimate the risk of nonSN metastases after neoadjuvant chemotherapy (NAC) in patients with SN metastasis before NAC. METHODS: This retrospective study included 217 consecutive patients who had received sentinel node biopsy (SNB) before NAC between February 2005 and December 2008. We compared clinicopathologic factors, including age, menopause status, nuclear grade, tumor size, estrogen-receptor(ER) and human EGFR-related 2 (HER2) receptor statuses, clinical response and pathological response between patients with nonSN metastasis and patients without nonSN metastasis after NAC. RESULTS: A mean of 2.0 SNs were identified in the 217 patients. One hundred seventy (78.3%) of 217 patients had SN metastasis and underwent axillary lymph node dissection (ALND) after NAC. Among those who had positive SN before NAC, micrometastasis were found in 18 of the 170 patients (11.1%) and macrometastasis in 152 patients (89.4%). After NAC, 44 (25.8%) of the 170 patients had nonSN metastasis ;2 patients (1.2%) with micrometastasis and 42 patients (24.7%) with macrometastasis. In the 44 patients with nonSN metastasis, all tumor size was more than 2cm. All patients with nonSN metastasis had HER2-positive primary breast cancer. There was no risk factor to predict nonSN metastasis after NAC in patients with SN metastasis before NAC. At a median follow-up time of 44 months, 5 patients (11.3%) with nonSN metastasis and 9 patients (7.1%) without nonSN metastasis developed recurrences. CONCLUSIONS: We could not identify the predictive factor of nonSN metastasis after NAC in patients with SN metastasis before NAC although our sample size was largest among studies which have been reported. This suggest that complete axillary lymph node dissection should be performed when patients had SN metastasis before NAC unless we could identify the group who have minimum risk for nonSN metastasis after NAC with positive SN before NAC.

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Nomogram for Predicting Loco-regional Recurrence in Patients Receiving Breast-conserving Surgery after Neoadjuvant Chemotherapy for Primary Breast Cancer N. Matsuda,[1]* N. Hayashi,[1] S. Ohde,[2] H. Yagata,[1] Y. Kajiura,[1] A. Yoshida,[1] K. Suzuki,[3] S. Nakamura,[5] H. Tsunoda,[4] H. Yamauchi.[1] *1. Department of Breast Surgery,St.Luke's International Hospital, Tokyo, Japan; 2. Center for Clinical Epidemiology,St.Luke's Life Science Institute, Tokyo, Japan; 3. Department of Pathology,St.Luke's International Hospital, Tokyo, Japan; 4. Department of Radiology,St.Luke's International Hospital, Tokyo, Japan; 5. Department of Breast Surgical Oncology,Showa University Shool of Medicine, Tokyo, Japan.*

Purpose:Neoadjuvant chemotherapy (NAC) has a possibility to reduce the volume of primary breast cancer and increases the rate of breast conservation surgery. However, the occurrence rate of loco-regional recurrence (LRR) may be higher in patients with Breast-conserving surgery after NAC than that in patients without NAC. The aim of current study was to determine the LRR rate in patients received breast-conserving surgery after NAC, and develop and validate nomogram for predicting LRR. Patients and Methods:We retrospectively determined the data of 520 consecutive primary breast cancer patients who were treated with breast-conserving surgery after NAC between 2001 and 2010. All patients received radiation therapy after the surgery. A multivariate Cox proportional hazards model was constructed to determine predictive variables of LRR. The model was validated for discrimination and calibration using bootstrap resampling. Results:A Median age was 49 years (range, 26 to 76 years). At a median follow-up period of 51 months (range, 4 to 111 months), 64 patients (12%) had developed LRRs. Variables that positively correlated with LRR were clinical T3 or T4, positive status for lymphovascular invasion, nuclear grade > 2, equal or more than 4 positive lymph nodes. The nomogram by using these variables for prediction of LRR demonstrated high concordance with area under the receiver operating characteristic (ROC) curve of 0.76 (95%CI:0.69-0.83). Bootstrapped validation beta coefficients of the predictors were identical with the original cohort beta coefficients. Conclusion:LRR rate in patients received breast-conserving surgery after NAC was acceptably low compared to that in patients without NAC as being reported. The nomogram which was developed with 4 clinocopathologic variables could predict loco-regional recurrence in patients received breast-conserving surgery after NAC for primary breast cancer with high reproducibility. This model may be useful to select patients who are not suitable to receive breast-conserving surgery due to high probability of loco-regional recurrence.

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Can Axillary Dissection be Avoided for Sentinel Node-positive Breast Cancer Patients who Fall Outside the Z0011 Inclusion Criteria? C.E. Pesce,* M.M. Stempel, S.M. Patil, H.S. Cody. *Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: The ACOSOG Z0011 trial has established that axillary lymph node dissection (ALND) is not required for breast cancer patients with 1-2 H&E positive sentinel nodes (SLN) treated with breast conservation and whole-breast RT, and has changed practice in many centers. Here we ask whether a policy of "no-ALND" can be extended beyond the Z0011 selection criteria to include SLN-positive patients treated by mastectomy. Methods: We reviewed our prospective SLN database over 10 years (7509 SLN procedures, 1997-2006) and identified 333 patients whose SLN were positive on routine H&E. For the breast conservation (BCT) and mastectomy patients, we compare event rates and treatment patterns, with a median followup of 71.5 months. Results: see Table Conclusions: Within the limits of our study design, we identify no significant differences in local, regional or distant relapse between patients treated by BCT vs. mastectomy, and between those who had vs. did not have ALND. These results suggest that a policy of "no-ALND" is reasonable for selected patients who fall outside the Z0011 selection criteria, but require confirmation in a prospective study.

	BCT (187 pts)		Mastectomy (146 pts)	
Recurrence	**ALND (123)**	**No ALND (64)**	**ALND (108)**	**No ALND (38)**
Local	2 (1.6%)	1 (1.6%)	1 (0.9%)	1 (2.6%)
Regional	0 (0%)	2 (3.1%)	1 (0.9%)	2 (5.3%)
Distant	7 (5.7%)	4 (6.3%)	6 (5.6%)	3 (7.9%)
Systemic therapy				
Chemotherapy	7/9 (77%)	4/7 (57%)	7/8 (88%)	4/6 (67%)
Hormonal	6/9 (67%)	3/7 (43%)	5/8 (63%)	2/6 (33%)
RT	8/9 (89%)	6/7 (86%)	3/8 (38%)	3/6 (50%)

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Metaplastic Breast Cancer has Worse Survival Outcomes Compared to Other Hormone Receptor Negative Breast Cancers M.L. Guye,* R.A. Nelson, T.H. Luu, L. Lai. *City of Hope, Duarte, CA.*

Background: Metaplastic breast carcinoma (MBC) is a rare breast neoplasm with both mesenchymal and epithelial components. Almost all are ER/PR negative. Optimal treatment remains ill-defined due to a limited understanding of the prognostic factors related to this rare subtype. The purpose of our study was to investigate outcomes of patients with metaplastic breast cancer compared to other hormone receptor negative (ER/PR-) infiltrating ductal carcinomas (IDC) and identify factors that may predict for improved outcome. Methods: The Surveillance Epidemiology and End Results registry was used to identify patients with ER/PR- metaplastic breast cancer and ER/PR- infiltrating ductal carcinoma treated with surgery between 2001 and 2008. In-situ and stage IV cases were excluded. Patients were evaluated by standard demographic, clinicopathologic, and treatment indices. Overall survival (OS) differences between groups were assessed by Kaplan-Meier method. Univariate and stepwise multivariate Cox proportional hazards analyses were performed. Results: Of the 53,291 patients with ER/PR- breast cancers, 779 (1.5%) had metaplastic subtype. The MBC patients had larger tumors, higher grade tumors, less axillary nodal involvement, and were more likely to receive mastectomy. Patients with metaplastic breast cancer had significantly worse 5-year OS when compared with ER/PR- IDC (69% vs. 77%, respectively; $p<0.0001$). Survival differences remained significant across all stage groups (Stage I-III). Stepwise multivariate analyses revealed that metaplastic histologic subtype was an independent poor prognostic factor (HR 1.30, 95% CI [1.12-1.51], $p=0.0007$). Other clinical factors that predict for worse OS on multivariate analysis are tumor size, tumor grade, and axillary lymph node involvement. Conclusion: Patients

with metaplastic breast cancer have worse outcomes compared to patients with hormone receptor negative infiltrating ductal carcinoma. Further investigation into prognostic factors, as well as development of predictive molecular markers, will better define this rare subset of breast cancers and potentially guide future treatment strategies.

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Clinical Utility and Effectiveness of Neoadjuvant Chemotherapy for Young Women with Breast Cancer R.A. Greenup,* A. Bardia, J. Buckley, M.S. Camp, M.A. Gadd, K. Hughes, S.B. Coopey, A. Niemierko, S.J. Isakoff, A.G. Taghian, M.C. Specht, B.L. Smith. *Surgical Oncology, Massachusetts General Hospital, Boston, MA.*

BACKGROUND: Neoadjuvant chemotherapy is a safe and effective alternative to adjuvant chemotherapy for women requiring systemic therapy for breast cancer. Benefits include improved rates of breast conservation therapy (BCT), assessment of tumor response to systemic therapy, and correlation of pathologic response with clinical outcome. There is little data on the utility and effectiveness of neoadjuvant chemotherapy in young women with breast cancer. We sought to determine pathologic response to neoadjuvant chemotherapy in women 40 and younger with breast cancer, and to identify predictors of pathologic response to neoadjuvant chemotherapy. METHODS: We performed an IRB-approved review of all women age 40 and younger who underwent neoadjuvant chemotherapy for primary breast cancer at our institution from 1996-2008. Patient and tumor characteristics, pre-treatment surgical plan and type of surgery were collected. Tumor subtype was categorized as HER2+, ER+/HER2-, or triple negative (TN). Complete pathological response (pCR) was defined as no residual invasive disease at pathologic review. Chi-square testing was utilized to compare non-parametric proportions. RESULTS: The cohort consisted of 83 women with a median age of 36 (range 24-40). Neoadjuvant chemotherapy was offered most commonly due to large tumor size 37%(31/83), presence of inflammatory breast cancer 11%(9/83), and extent of disease 8%(7/83). The overall pCR rate was 34%. Women with HER2+ tumors were more likely to achieve pCR than HER2- tumors (11/22 vs 17/61, 50% vs 28%, p = 0.06). There was no difference in pCR rate between ER+ and TN tumors (13/46 vs 4/15, 28% vs 27%). Among patients with BRCA gene mutations, 5/6 (83%) had a pCR following neoadjuvant chemotherapy. When neoadjuvant chemotherapy was offered to allow an attempt at BCT, 27/32 (84%) achieved breast-conservation, while 5/32 (16%) ultimately required mastectomy. CONCLUSIONS: Neoadjuvant chemotherapy is effective in breast cancer patients age 40 and younger, with high pCR rates and reasonable rates of breast conservation. Highest rates of pCR were seen among patients with HER2+ tumors and among BRCA gene mutation carriers.

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Correlated Breast Cancer Subtypes and Expression of CD47 in BM Predicts Recurrence M. Nagahara,[1]* K. Sugihara,[1] M. Mori.[2] *1. Tokyo Medical and Dental University, Graduate School of Medical and Dental Science, Tokyo, Japan; 2. Osaka University, Graduate School of Medicine, Osaka, Japan.*

Introduction: The biological subtypes of breast cancer have shown the prognostic features. Focused on CD47 expression in bone marrow (BM), we found the correlation between breast cancer subtypes and CD47 expression in BM, which may indicate important implications for prognostic factor. Experimental Design: Quantitative real-time PCR was used to evaluate CD47 mRNA expression in bone marrow (BM) and in peripheral blood (PB) from 452 cases of invasive ductal carcinoma of breast cancer. ER, PR, and Her2 scores were obtained from immunohistochemistry (IHC) staining, and Her2 FISH analysis conducted for IHC 2+. Results: According to ER, PR, and Her2 statuses, the groups of Her2 enriched (ER- and PR- and Her2 3+) and triple negative (ER- and PR- and Her2-) were divided (n=38 and 72). The 5 years disease free survival rates in each subgroup were as followed: p=0.0004; ER+ and PR+ and Her2- 0.94, ER+ and/or PR+ or- and/or Her2+ or- 0.16, Her2 enriched 0.23, triple negative 0.34). In patients with high levels of CD47 expression in the BM, survival was significantly poorer compared to patients with low levels of CD47 expression (DFS of Her2 enriched group: P=0.003, DFS of triple negative group: P=0.02). Furthermore, high CD47 expression group in a multivariate analysis showed significance as an independent variable for poorer prognosis in DFS (P = 0.02). In the PB, however, high CD47 expression in patients was not an independent and significant prognostic factor for DFS and OS in a multivariate analysis. Conclusions: We confirmed that overexpression of CD47 in BM correlated with the aggressiveness of Her2 enriched and triple negative subgroups. CD47 is a useful prognostic biomarker for predicting survival of Her2 enriched and triple negative subgroups in breast cancer.

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Biology, Treatment, and Outcome in Very Young and Older Women with DCIS R. Alvarado,* S.A. Lari, R.E. Roses, B.D. Smith, W. Yang, E.A. Mittendorf, B.K. Arun, A. Lucci, G.V. Babiera, J.L. Wagner, A.S. Caudle, F. Meric-Bernstam, R. Hwang, I. Bedrosian, K.K. Hunt, H.M. Kuerer. *Breast Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX.*

Introduction: Ductal carcinoma in situ (DCIS) appears to vary in outcome according to biology at presentation. This study examines a modern cohort of women in order to identify potential differences in clinical presentation, treatments, and outcome based on age. Methods: From 1996 to 2009, 2,037 patients with pure DCIS were treated. Clinical presentation, pathologic factors, type of surgery and adjuvant therapy, and local-regional recurrence (LRR) rates among age groups were compared and analyzed. The median length of follow-up was 5.2 years. Results: There were 132 (6.5%) patients under age 40, 1690 (83%) age 40-70, and 215 (10.5%) were >70 y old. As shown in the table, younger patients (< 40) were significantly more likely than patients older than 40 to have a family history of breast and ovarian cancer, to present with clinical symptoms, have higher nuclear grade DCIS, to undergo mastectomy with immediate reconstruction, and to have a contralateral prophylactic mastectomy (P<0.05). Older patients (>70) were significantly less likely to use adjuvant radiotherapy and tamoxifen (P<0.05) and significantly more likely to undergo lumpectomy (P=0.014). No significant differences were found in the mammographic or pathologic size of the lesion, ER-status, or necrosis based on age. On multivariate analysis, younger age (< 40), larger size DCIS (≥ 1.5 cm), and no use of radiotherapy were significant independent predictors of LRR. For women receiving radiotherapy, the five-year rates of LRR were not significantly influenced by age. Among women who did not receive radiotherapy, the five-year rate of LRR was significantly higher among younger patients. Conclusions: Young onset DCIS is more often higher-grade and diagnosed on the basis of clinical findings. Younger patients are more likely to opt for, or require mastectomy with immediate reconstruction, although conservative surgery with radiation is appropriate. In the absence of radiotherapy, conservative surgery is associated with an unacceptably high rate of local regional recurrence in very young women.

Table. Characteristics, Treatment and Outcome of DCIS by Age

	Patients < 40 y, N (%)	Patients 40 – 70 y, N (%)	Patients > 70 y, N (%)	*P*-value < 40 vs. >40 y	*P*-value < 70 vs. > 70 y
Any Family history of Breast and/or Ovarian Cancer					
	85 (64.4)	794 (47.0)	84 (39.1)	**0.001**	**0.011**
Initial Presenting Signs					
Clinical	74 (56.1)	233 (13.9)	32 (15)		
Radiological	58 (43.9)	1,446 (86.1)	181 (85)	**0.001**	0.476
Nuclear Grade					
I	6 (4.7)	162 (9.8)	26 (12.2)		
II & III	121 (95.3)	1,491 (90.2)	188 (87.9)	**0.049**	0.206
Surgery					
Lumpectomy	56 (42.4)	1,015 (60.1)	145 (67.4)		
Mastectomy	76 (57.6)	675 (39.9)	70 (32.6)	**0.001**	**0.014**
Use of Immediate Breast Reconstruction among patients w/ Mastectomy					
	64 (82.1)	449 (66.4)	11 (15.7)	**0.001**	**0.001**
Use of Contralateral Mastectomy (Prophylactic)					
	28 (21.2)	118 (7.0)	4 (1.9)	**<0.001**	**0.001**
Use of Adjuvant Tamoxifen and Adjuvant Radiotherapy (BCT only)					
	19 (67.9)	408 (75.4)	29 (47.5)	0.584	**<0.001**
5-year LRR rate (Mastectomy; n=821)					
	0%	1.3%	0%	0.427	0.434
5-year LRR rate (BCT with radiotherapy, n=977 patients)					
	6.4%	2.1%	2.6%	0.143	0.701
5-year LRR rate (BCT without radiotherapy, n=239 patients)					
	22.9%	8.0%	3.1%	**0.006**	0.235

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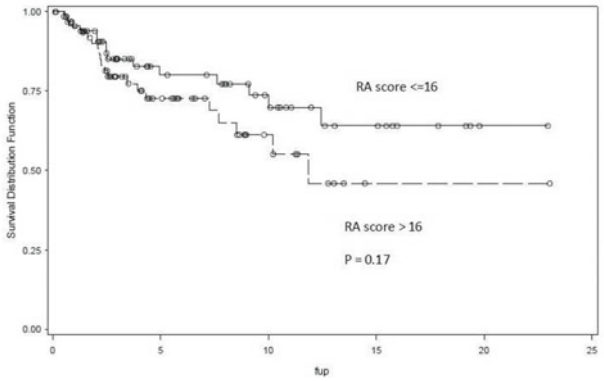
Common Breast Cancer Risk Alleles and Lobular Carcinoma In Situ (LCIS) S. Koslow,* C. Manschreck, S. Patil, J. Vijai, S. Muhsen, A. Park, M. Robson, T. King. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Background: Women with LCIS have an 8-10-fold increased risk of breast cancer (BC), yet only 15-20% of women with LCIS develop BC. We hypothesized that common genetic variants associated with BC in the general population would be associated with development of cancer in women with LCIS. Methods: From a prospective ascertainment of 998 women in surveillance following a diagnosis of LCIS, whole blood samples were available for 197 (20%) patients. Germline DNA was extracted and genotyped at 15 previously published breast cancer risk loci using the Sequenom massARRAY iPLEX platform. A cumulative risk allele (RA) count for each patient was calculated by assigning a score of 0 (homozygous for non-RA), 1 (heterozygous for RA) or 2 (homozygous for RA) at each risk locus. Only samples that were informative at all 15 loci were included. BC-free survival (BCFS) was calculated by Kaplan-Meier (KM) in women not receiving chemoprevention (CP). Multivariate Cox regression was performed to evaluate the association of RA count with BCFS adjusted for age & breast density. Results: 193/197 subjects were successfully genotyped, including 38 patients who developed breast cancer at a median time of 29 months (range 6-149mos), 120 patients cancer-free without CP (median f/u 64mos, range 1-276mos) and 36 patients cancer-free with CP (median f/u 80mos, range 13-247mos). The mean age at diagnosis of LCIS was 50yrs (range 28-73yrs) and there was no difference between the 3 groups. RA scores were evaluable for 168/193 (87%) patients. Median RA score was 16 (range 9-22). Among pts with a RA score <= 16, 5yr BCFS was 0.80 (95% CI 0.66-0.89) as compared to 0.73 (95% CI 0.59- 0.83) among pts with a RA score > 16 (Figure - KM curve). Adjusting for breast density, on Cox regression using RA score <= or >16, the hazard ratio (HR) for breast cancer in women with LCIS was 1.81 (95% CI 0.91-3.62), p=0.09. Conclusions: An increased number of risk alleles were associated with a greater probability of developing breast cancer, but this did not reach statistical significance. Risk stratification among women with LCIS remains a significant challenge in clinical practice.



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Characteristics, Patterns of Treatment and Outcome of Adenoid Cystic Carcinoma of the Breast: Analysis of 933 Cases from the National Cancer Data Base C.M. Pezzi,[1]* J.M. Greif,[2] V. Klimberg,[3] N. Kulkarni,[1] L. Bailey,[2] S. Korourian,[3] M. Zuraek.[4] *1. Surgery, Abington Memorial Hospital, Abington, PA; 2. Bay Area Breast Surgeons, Inc., Oakland, CA; 3. University of Arkansas for Medical Sciences, Little Rock, AR; 4. Alta Bates Summit Medical Center, Berkeley, CA.*

Introduction: Adenoid cystic carcinoma (ACC) is a rare subtype of breast cancer. Limited data has suggested a favorable prognosis with infrequent metastasis. We hypothesized that in comparison to infiltrating ductal carcinoma (IDC), ACC has different characteristics, patterns of treatment and prognosis. Methods: Patients with ACC and IDC reported to the National Cancer Data Base from 1998-2008 were reviewed for patient age, ethnicity, tumor size, nodal status, TNM stage, grade, and initial treatment. Survival analysis was performed for patients from 1998-2003. Hormone receptor status was examined in patients from 2004-08. Data were analyzed using the Chi-square test and by non-parametric Wilcoxon rank-sum test. Survival rates were calculated using the Kaplan-Meier method and compared by Log-rank test. Results: 933 patients with ACC and 729,938 with IDC were identified. No differences were found for incidence by race/ethnicity (p=0.97). The group with ACC was older (median 60 years vs. 58 years), had larger tumors (median 18mm vs. 16mm), more grade 1 tumors (46% vs. 18%), was less likely to undergo axillary lymph node evaluation (75.9% vs. 96.3%), had fewer node-positive patients (5.1% vs. 35.5%), had fewer estrogen receptor positive tumors (15.4% vs. 75.6%), had fewer progesterone receptor positive tumors (13.3% vs. 65.2%), and underwent breast-conserving surgery more often (69.8% vs. 59.8%). Chemotherapy was used less often for ACC (11.3% vs. 46.4%), as was hormonal therapy (9.1% vs. 42.3%). These differences were all statistically significant (p<0.0001). With a mean follow-up of 57.9 months, five-year overall survival (OS) was 88% for ACC vs. 84% for IDC (p=0.02). There was no difference in OS for Grade 1 (ACC,91% vs. IDC,92%; p=0.50) and for Stage I (ACC,90% vs IDC,91%; p=0.93). Conclusions: Compared with IDC, ACC have different characteristics (lower grade, hormone negative, node-negative), are treated differently (less axillary surgery, fewer mastectomies, less chemotherapy, and less hormonal therapy), and do have an improved prognosis, with 88% five-year survival rates, despite less aggressive treatment.

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Patient and Process Factors Associated with Late-stage Breast Cancer Diagnosis in Safety Net Patients O.M. Fayanju,[1]* D.B. Jeffe,[2] L. Elmore,[1] D.N. Ksiazek,[2] J.A. Margenthaler.[1] *1. Surgery, Washington University in St. Louis, St. Louis, MO; 2. Department of Medicine, Washington University in St. Louis, St. Louis, MO.*

INTRO In 2007, we reviewed our city's Safety Net (SN) breast cancer referral process and found that SN patients were nearly 4 times as likely as non-Safety Net (NSN) patients to have late-stage disease at diagnosis. As a result, changes were made to improve efficiency of referral to our city's comprehensive cancer center and to increase screening mammography rates among SN patients. We sought to determine whether personal and process factors that might contribute to late-state diagnosis would differ by type of referral (SN vs. NSN). METHODS From September 2008 to June 2010, SN patients with any-stage (0-IV) breast cancer and NSN patients with late-stage (IIB-IV) disease were identified prospectively during their initial consultations at our cancer center. Patients were invited to participate in 45-60 minute telephone interviews. Clinical data were obtained from medical records. We examined differences in factors potentially associated with late-stage breast cancer by type of referral using chi-square tests; two-tailed p<0.05 was considered significant. RESULTS Fifty-seven women (SN-referred: 33/47 invited [70%], mean age 53 [30-68]; NSN-referred: 24/35 invited [69%], mean age 53 [33-76]) completed interviews. Fifty-two percent of SN-referred patients were diagnosed with late-stage disease compared with 100% of NSN patients (by design). Compared with NSN late-stage patients, SN late-stage patients were more likely to be African-American (83% vs. 21%, p<0.001) and to have an annual household income <$25,000 (89% vs. 38%, p<0.001); they were less likely to be married/partnered (22% vs. 79%, p<0.001), to have any insurance (61% vs. 96%, p<0.005), and to have a primary care physician (25% vs. 67%, p=0.012). Finally, SN patients were less likely to have sought medical attention promptly (i.e., <1 week) upon realizing they had concerning breast findings (50% vs. 79%, p=0.047). CONCLUSIONS SN patients presented with higher-than-expected rates of late-stage disease even after implementing changes in the referral process. Findings illustrate the need to facilitate post-screening follow-up, education, and better primary care access for this vulnerable patient population.

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Does Breast Tumor Heterogeneity Necessitate Further Immunohistochemical Staining on Surgical Specimens? L.T. Greer,[2]* M. Rosman,[1] W. Mylander,[1] A. Kovatich,[2] J. Hooke,[2] J.A. Wareham,[1] J. Campbell,[2] W. Liang,[1] R. Buras,[1] C. Shriver,[2] L. Tafra.[1] *1. Breast Center, Anne Arundal Medical Center, Annapolis, MD; 2. Walter Reed National Military Medical Center, Bethesda, MD.*

Introduction: Prognostic and predictive tumor markers (ER, PR, HER2, Ki-67) in breast cancer are most commonly performed on core needle biopsies (CNB) of the primary tumor. Because treatment recommendations are influenced by these markers, it is imperative to verify strong concordance

between tumor markers derived from IHC testing on CNB specimens and the corresponding surgical specimens (SS). Methods: A prospective study was performed on 132 women (151 samples) with breast cancer diagnosed from January 2009 to March 2011. Tumor type, grade, ER, PR, HER2, Ki67 expression by IHC were retrospectively analyzed in the CNB and SS. Contingency tables and agreement modeling were performed to generate Kappa values. ER% and PR% were calculated based on positivity being >1%, HER2 was considered positive if CNB showed 2+(FISH positive) or 3+ but on SS was based on 3+ only (no FISH performed on SS). Results: There was substantial agreement between the CNB and SS for tumor type, ER%, PR%, HER2; moderate agreement for grade; and fair agreement for Ki67% (see Chart). The CNB contained higher percentages of ER, PR and Ki67 than the SS. Distinct molecular subtypes (tumor heterogeneity) by H&E and IHC were noted in the SS of 14 subjects (11%). These patients had multiple IHC testing performed on different areas of tumor. In 3 of these subjects (21%), HER2 was found to be positive in an area of the SS but was negative on the CNB. No cases were seen where ER or PR were negative on CNB but became positive in the SS. However, 2 subjects in the heterogeneous group had distinctly different regions in their tumor where one was ER positive and another was ER negative. Conclusion: The heterogeneous distribution of antigens in breast cancer tumors raises concern that the CNB may not adequately represent the true biologic profile in all patients. There is strong concordance for tumor type, ER, and PR between CNB and SS; however, HER2 activity does not appear to be adequately detected on CNB in patients with heterogeneous tumors. This data highlights that the IHC testing on the CNB alone may not be adequate to tailor targeted therapy in all patients.

Biomarker	# Agreements	Kappa (κ)	Landis-Koch Agreement Grade	95% CI
Tumor Type	124/151 (82%)	0.66	Substantial	(0.55, 0.77)
Histologic Grade	84/133 (63%)	0.44	Moderate	(0.31,0.56)
ER%	142/151 (94%)	0.73	Substantial	(0.56,0.89)
PR%	134/151 (89%)	0.69	Substantial	(0.55,0.82)
HER2	128/134 (96%)	0.68	Substantial	(0.43,0.92)
Ki67 %	52/119 (44%)	0.21	Fair	(0.10, 0.31)

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Oncologic Outcome of Nipple-sparing Mastectomy for Breast Cancer Treatment: A Retrospective Study in 248 Patients in a Single Institution A. Koike,* K. Tsugawa, T. Uejima, K. Tsuchiya, Y. Kojima, A. Shimo, R. Hayami, H. Kawamoto, Y. Yabuki, H. Ogata, M. Fukuda. *Division of Breast and Endocrine Surgery, St. Marianna University School of Medicine., Kawasaki, Kanagawa, Japan.*

Introduction; Nipple-sparing mastectomy (NSM) is one of the available surgical options for breast cancer, but the oncologic safety is controversial. However, some investigators had reported that no difference in the local recurrence rates and overall survival rates compared with the conventional total mastectomy. We evaluated the oncologic outcome of 248 cases underwent NSM, and discuss the indication for NSM for primary breast cancer. Methods; A retrospective chart review was performed of 248 patients undergoing NSM during January 2000 to March 2010. In our institute, the indication of NSM is no suspicious infiltration to nipple-areolar complex by preoperative MRI imaging, and negative subareolar biopsy by intraoperative frozen section. We collected data included patient age, size of tumor, number of metastatic lymph node, histologic type, subtype, biomarker, and adjuvant therapies, analyzed as the risk factors of the nipple-areola recurrence. Results; Twenty-three patients underwent nipple-areolar complex removal because of positive biopsies. Ninety-five patients underwent reconstruction. Two cases (0.8%) had the nipple loss complications due to nipple necrosis. The local recurrence rate after NSM was 6.7%(15 cases), and it was similar to conventional total mastectomies in the same periods, 6.2%(57 in 869 cases). Furthermore, the localized nipple-areolar recurrence rate after NSM was 3.6%(8 cases). We had confirmed these subareolar biopsies were negative both on the frozen and permanent histologic diagnosis. Relapse-free survival was mean 27(4-90) months in median follow up 37 months. The HER2-enriched tumors were significantly increased to the nipple-areolar recurrences. Additionally, young age (< 40), large tumor (>5cm), and triple negative tumor were also increased, too. Nevertheless, the sites of nipple recurrence were able to be excised easily, and the good cosmetic results were kept in the implant reconstruction cases. Conclusion; The nipple-areolar recurrence rate as 3.6% is low. The NSM can be performed safety with the low complications. The NSM appears to be oncologically safe with superior cosmesis.

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Does Trastuzumab Containing Neoadjuvant Chemotherapy Impact In Situ Carcinoma? E. Diego,* G.M. Ahrendt, K.P. McGuire, R.R. Johnson, P. Badve, R. Bhargava. *UPMC-Magee Womens Hospital, Pittsburgh, PA.*

Background: Herceptin-based neoadjuvant chemotherapy (NAC) is frequently used in ERBB2+ (HER2+) breast cancer to facilitate breast conservation. Invasive ductal carcinoma (IDC) is frequently associated with a component of DCIS. In >90% of patients with HER2+ IDC, the DCIS component is also HER2+ (Ann Clin Lab Sci. 2007;37:127-134). The aim of the study was to assess the pathologic response of DCIS in patients receiving neoadjuvant chemotherapy for HER2+ invasive breast cancer. We hypothesized that trastuzumab containing chemotherapy will result in regression of the adjacent in-situ carcinoma. Methods: The institutional pathology database was reviewed and 102 patients with HER2+ invasive cancers treated from 2007-2010 with trastuzumab-based NAC with subsequent excision were identified. Most patients received combination chemotherapy consisting of taxane, carboplatinum, and trastuzumab (TCH). Core biopsy and surgical pathology reports were analyzed for the presence of DCIS at the time of diagnosis and following NAC. Results: Thirty-seven of 102 patients demonstrated a complete pathologic response (pCR), defined as absence of invasive cancer in the breast specimen and lymph nodes. Eighteen of 37 patients with a pCR (49%) had DCIS in association with IDC on percutaneous pre-treatment biopsy. Eleven of these 18 (61%) had no residual DCIS on post-treatment resection specimens. Sixty-five patients failed to show pCR. Thirty-two of these 65 patients (49%) had DCIS in association with IDC on percutaneous pre-treatment biopsy. Only 5 of these 32 patients (16%) had no residual DCIS on post-treatment resection specimen. The difference between pCR and no-pCR group with respect to resolution of DCIS was statistically significant ($p = 0.0016$). Conclusions: The therapeutic effect of trastuzumab on HER2+ invasive carcinoma potentially extends to associated in-situ disease. These findings may translate into improved outcomes with fewer re-excisions for positive margins or smaller volume resections in patients receiving trastuzumab for invasive disease.

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Trends in Postmastectomy Radiation Therapy for Patients with T3 or N2 Disease K. Yao,[1]* N. Hou,[2] D.J. Winchester,[1] E. Barrera,[1] N. Jaskowiak,[2] D.P. Winchester,[1] D. Huo.[2] *1. Surgery, NorthShore University HealthSystem, Evanston, IL; 2. University of Chicago, Chicago, IL.*

Background: NCCN and ASCO guidelines recommend postmastectomy chest wall radiation (PMRT) for patients with pT3 or pN2 disease. We examined the secular trends and correlates for PMRT utilizing the National Cancer Data Base (NCDB). Methods: A total of 72,753 invasive breast cancer patients from 1998-2007 were studied. Patients with pT4 tumors, neoadjuvant treatment, and stage IV disease were excluded. Pearson Chi–square tests and logistic regression models were used to analyze the factors related to PMRT use. Results: The percentage of patients undergoing PMRT increased from 50% in 1998 to 62% in 2003, and then decreased to 56% by 2007. This secular trend persisted when adjusting for the covariates as noted below ($p<0.001$). PMRT utilization was 55% at community cancer centers, 58% at comprehensive community centers, and 55% at academic/teaching centers ($p<0.001$). PMRT varied significantly by facility location, with the highest rates in the Northeast (68%) and lowest in the West (47%). Using a mixed effect model to account for region, there was a persistent 18% variation in the use of PMRT. Patients 80 years or older were 71% (OR=0.29, 95% CI 0.27-0.31) and 70-79 year-olds 46% (OR= 0.54, 95% CI 0.51-0.58) less likely to undergo PMRT then patients <40 years old. Hispanic and African Americans were 24% and 21% less likely (OR=0.76, 95% CI 0.71-0.81 and OR=0.79, 95% CI 0.75-0.83, respectively) to undergo PMRT then whites and Asians (OR=1.17, 95% CI 1.06-1.29) 17% more likely to undergo PMRT. Patients with private or managed care insurance were 60% more likely to undergo PMRT than non-insured patients (OR=1.6, 95%CI 1.50-1.83) whereas Medicaid patients were 20% (OR=1.19, 95% CI 1.08-1.32) more likely to receive PMRT then uninsured. High comorbidity index predicted a lower rate of PMRT. Tumor grade and estrogen receptor were not significant predictors. In multivariate logistic regression, the aforementioned factors remained significantly associated with PMRT utilization. Conclusions: There is low compliance with ASCO and NCCN guidelines for PMRT suggesting that socioeconomic and geographical barriers prevent appropriate delivery of care.

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High Local Control Rate in the Combination of Surgery, Reirradiation and Hyperthermia for Radio-induced Angiosarcoma of the Chest Wall M. Linthorst,[1]* B.N. Van Geel,[2] L.A. Baartman,[3] B. Oei,[4] W. Ghidey,[5] C. Van der Zee.[1] *1. Department of Radiation Oncology, Hyperthermia Unit, Erasmus Medical Center/Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 2. Department of Surgical Oncology, Erasmus Medical Center/ Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 3. Department of Radiation Oncology, Erasmus Medical Center/Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 4. Department of Radiation Oncology, Verbeeten Institute, Rotterdam, Netherlands; 5. Department of Trial and Medical Statistics, Erasmus Medical Center/Daniel den Hoed Cancer, Rotterdam, Netherlands.*

Background: Management of radiation-induced angiosarcoma (RIA) has a poor prognosis due to a high percentage of local failures. The efficacy and side effects of reirradiation and hyperthermia alone, or combined with preceding or following surgery were reviewed in patients with RIA of the chest wall. Patients and Methods: Outcome in RIA of 29 breast cancer patients and 1 patient with melanoma after previous breast-conserving therapy (n = 22), mastectomy with irradiation (n = 7) and axillary lymph node dissection with irradiation (n = 1), treated from 2000 till 2011 was reviewed. Treatment consisted of surgery followed by reirradiation and hyperthermia (n = 13), reirradiation and hyperthermia followed by surgery (n = 3) or reirradiation and hyperthermia (n = 14). The median age was 68 years. Patients were treated with a radiation dose of 32-50 Gy (mean 34 Gy) and 2-6 hyperthermia treatments (mean 4). Hyperthermia was given once or twice a week after the radiotherapy. Results: Acute grade 3 toxicity (CTCAEv3.0) was observed in one patient. The median overall survival was 11 months (range 1-78 months). After reirradiation and hyperthermia the complete response was 47.0%. In the subgroup of patients without surgery 3 months, 1- and 3-year local control was 38.5%, 19.2% and 9.6%, respectively. In the subgroup of patients with surgery, 3 months, 1- and 3-year local control was 93.7%, 50.2% and 50.2%, respectively. Conclusion: The present study shows that reirradiation and hyperthermia when combined with surgery results in a high local control rate in patients with RIA.

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A Positive Ultrasound Guided Needle Biopsy of Axillary Nodes Predicts a Higher Stage of Axillary Disease In Breast Cancer B.A. Boone,[1]* C. Huynh,[1] M.L. Spangler,[2] J. Sumkin,[2] R. Johnson,[1] K.P. Mcguire,[1] A. Soran,[1] G.M. Ahrendt.[1] *1. Surgery, University of Pittsburgh, Pittsburgh, PA; 2. University of Pittsburgh, Pittsburgh, PA.*

Introduction The results of the ACOSOG Z0011 trial suggest that axillary lymph node dissection (ALND) may be omitted in select patients with a positive sentinel lymph node (SLNB). It is unknown if the findings of ACOSOG Z0011 can be applied to patients with a positive axillary lymph node on ultrasound guided FNA or core needle biopsy (USNB). The percentage of these patients that will have further node involvement on ALND is unknown. We hypothesized that patients with a positive USNB will have higher stage axillary disease than patient with a positive SLNB. Methods An institutional breast cancer registry was searched to identify women with invasive cancer and a positive USNB or SLNB who had a completion ALND from 2005 to 2010. Patients who received neoadjuvant chemotherapy were excluded. Electronic health records were retrospectively reviewed to collect clinical and pathologic staging data. Chi squared test and one way ANOVA was used to evaluate data. Results 199 patients with a positive USNB and 434 patients with a positive SLNB were eligible for the study. All patients had completion ALND. Results are listed in Table 1. Patients with positive USNB were significantly older, had larger tumors, and were more likely to be ER-, PR- and Her2/neu + than SLNB positive patients. Additional positive nodes were found on axillary dissection in 93.9% of patients in the USNB group and only 34.6% of patients in the SLNB group ($p<0.05$). Patients who had a positive USNB had a much higher rate of N2 (33.2% vs. 12.4%, $p<0.05$) and N3 (17.1% vs. 3.9%, $p<0.05$) disease compared with positive SLNB patients. Completion ALND resulted in a higher N stage in 45% of USNB patients and 14% of SLNB patients. Conclusion Patients with invasive breast cancer who have a positive node on USNB have a significantly higher stage of axillary metastatic disease compared with patients with a positive SLNB. Based on these results, completion ALND is recommended in patients with a positive USNB. Further study to identify characteristics that predict a lower burden of axillary metastasis in these patients is warranted.

Table 1

		SLNB n=434	USNB n=199	p
Age	Mean	56.3	58.7	<0.05
	Median(Range)	55 (26-86)	59 (30-89)	
T	1	227 (52.4%)	54 (27.1%)	<0.05
	2	162 (37.4%)	114 (57.3%)	
	3	43 (9.9%)	30 (15.1%)	
	4	1 (0.2%)	1 (0.5%)	
	Mean	1.58	1.89	
	Median	1	2	
N	1	363 (83.6%)	99 (49.7%)	<0.05
	2	54 (12.4%)	66 (33.2%)	
	3	17 (3.9%)	34 (17.1%)	
	Mean	1.2	1.7	
	Median	1	1	
ER	Pos	389 (90.5%)	156 (78.8%)	<0.05
	Neg	41 (9.5%)	42 (21.2%)	
PR	Pos	366 (85.1%)	149 (24.7%)	<0.05
	Neg	64 (14.9%)	49 (75.3%)	
Her2	Pos	65 (15.1%)	40 (20.2%)	<0.05
	Neg	327 (76.0%)	128 (64.6%)	
	Equ	38 (8.8%)	30 (15.2%)	
Addl. + Nodes on ALND	n(%)	150 (34.6%)	187 (93.9%)	<0.05
	Mean	1.1	4.7	
	Median	0	3	
Total + Nodes	Mean	2.5	5.7	<0.05
	Range	1-27	1-37	
Total Nodes Evaluated	Mean	17.2	17.8	0.12
	Range	5-39	6-43	

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Complication Rates following Mastectomy with Reconstruction in Malignant and Prophylactic Breasts: A Matched Cohort Study A.K. Seth,[1]* E.M. Hirsch,[1] N.M. Hansen,[2] N.A. Fine.[1] *1. Northwestern University, Feinberg School of Medicine, Division of Plastic Surgery, Chicago, IL; 2. Northwestern University, Feinberg School of Medicine, Lynn Sage Comprehensive Breast Center, Chicago, IL.*

Introduction: Contralateral prophylactic mastectomy with reconstruction has become increasingly common among breast cancer patients. However, the risk of performing an additional procedure on otherwise benign tissue remains unclear. This matched cohort study evaluates complication rates for malignant and prophylactic breasts in patients undergoing bilateral mastectomy with reconstruction. Methods: Retrospective review of 897 consecutive patients from 4/1998-8/2008 at one institution yielded 203 that underwent bilateral mastectomy and implant reconstruction for unilateral breast cancer. Only patients with a benign prophylactic breast and unilateral disease on pathology were included. Matched cohorts were formed by comparing each patient's malignant breast to its prophylactic counterpart. Relevant clinical factors and follow-up were recorded. Complications were calculated per breast and categorized by end-outcome, including non-operative (no further surgery), operative (further surgery except explantation), and explantation. Fisher's exact test and multiple linear regression were used for analysis. Results: With each patient's breasts internally matched, the cohorts (n=203 breasts/group) were clinically identical. Mean follow-up was 36.2 months. There were no significant differences in complication rates between malignant and prophylactic breasts, including non-operative (8.9% v. 6.9%), operative (7.9% v. 8.4%), explantation (5.9% v. 5.4%), and total complications (10.3% v 11.8%). Regression analysis revealed that advanced age (>50 years), obesity (body mass index>30), and smoking were independent risk factors for having a complication, particularly explantation, in both cohorts ($p<0.05$) (Table 1). Conclusions: Our review demonstrates that contralateral prophylactic mastectomy is not without consequence, incurring the same complication risk as the cancerous breast. These outcomes are particularly evident in patients with other defined risk factors. Contralateral prophylactic mastectomy should be performed following both careful patient selection and a thorough preoperative discussion of its potential oncologic benefits and operative risks.

Table 1. Multiple linear regression

TOTAL COMPLICATIONS						
	Prophylactic			Cancer		
Characteristic	OR	95% CI	p	OR	95% CI	p
Age>50	3.24	1.35-7.75	0.006	3.75	1.47-9.57	0.003
BMI>30	3.38	1.34-8.49	0.007	2.64	1.01-7.10	0.048
Smoking	3.93	1.34-11.5	0.009	4.80	1.61-14.3	0.003
ACD	2.13	0.81-5.60	0.12	0.73	0.20-2.60	0.62
Tumescence	0.83	0.35-2.00	0.68	1.64	0.66-4.07	0.28
EXPLANTATION						
	Prophylactic			Cancer		
Characteristic	OR	95% CI	p	OR	95% CI	p
Age>50	5.87	1.50-22.9	0.004	6.60	1.73-25.3	0.002
BMI>30	4.33	1.24-15.1	0.01	5.40	1.63-17.9	0.002
Smoking	6.29	1.67-23.8	0.003	5.50	1.50-20.3	0.005
ACD	1.88	0.47-7.45	0.40	0.39	0.05-3.15	0.36
Tumescence	4.07	1.05-15.8	0.03	1.45	0.45-4.66	0.53

OR: odds ratio; CI: confidence interval; BMI: body mass index; ACD: acellular dermis

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Single Center Experience with Disseminated Tumor Cells as Predictors of Outcome in Patients with Stage I-III Breast Cancer

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Introduction: Published studies from Europe have shown the presence of disseminated tumor cells (DTCs) to independently predict outcomes in patients with non-metastatic breast cancer. The purpose of this study was to assess the experience with DTCs at a tertiary cancer center and to see if these cells indeed predict outcomes in patients with stage I-III breast cancer. Methods: Clinical stage I-III breast cancer patients seen at a single tertiary cancer center provided consent to participate in an IRB-approved study involving collection of bone marrow (5 ml x 2 tubes) at the time of surgery for their primary breast cancer. DTCs were assessed by anti-CK antibody cocktail (AE1/AE3, CAM5.2, MNF 116, CK 8 and 18) following cytospin. A positive result was defined as the presence of one or more cells per 5 ml of bone marrow. Statistical analyses used chi-square and Fischer's exact tests. Results: Three hundred and sixty-six patients were prospectively enrolled. Mean age was 53 years. Median follow-up was 32 months. DTCs were identified in 109 patients (30%). Ten percent of patients with DTCs (11/109) and 3% of patients without DTCs (8/257) died.(P=0.009) Overall survival (OS) in patients with DTCs was 30 months vs. 31 months in those without DTCs. DTCs did not predict relapse free survival.(P=NS) On multivariate analysis the presence of DTCs was an independent predictor of worse overall survival.(P<0.0001) No correlation was observed between the presence of DTCs and lymph node metastases and/or other clinicopathologic variables. Discussion: The presence of DTCs was an independent predictor of worse OS in patients with stage I-III breast cancer.

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Recurrences following Mastectomy for Ductal Carcinoma in Situ

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Background: Mastectomy reduces the risk of local recurrence of all breast cancers. Our goal was to evaluate recurrence following mastectomy for ductal carcinoma in situ (DCIS). Methods: An IRB-approved, single institution prospective database of patients treated with mastectomy for DCIS from 1997-2010 was reviewed. Patients with ipsilateral invasive disease on final pathology were eliminated. Clinicopathologic data was collected; locoregional recurrences (LRR) and distant metastases were identified. Results: Four hundred thirty-nine patients underwent mastectomy for DCIS as primary (400 patients, 91.1%) or recurrent (39 patients, 8.9%) breast cancer. Thirty patients (6.8%) had a history of contralateral breast cancer; 51 (11.6%) had synchronous bilateral cancers. Median age was 55.8 years (range 23-91); median follow-up was 28 months (range 0-195). Mastectomy was performed for extensive disease in 162 (36.1%), patient choice in 157 (35%), failed breast conservation in 74 (16.5%), prior radiation (36 breast cancer, 3 Hodkgin's lymphoma) in 39 (8.7%), and unknown for 17 (3.8%). DCIS grade was available for 441 specimens (98.2%); 46 (10.4%) were low, 154 (34.9%) intermediate, and 241 (54.6%) high grade. Hormone receptor status was available for 241 specimens (52.8%) of which 176 (73%) were estrogen receptor positive and 135 (56%) progesterone receptor positive. Four hundred thirteen (92%) underwent sentinel lymph node biopsy (SLNB); 3 (0.7%) had nodal micrometastases. After mastectomy, 21 patients had margins <2 mm; 2 received radiation. Three hundred ninety-nine patients were treated with primary mastectomy for pure DCIS; 5 (1.25%) developed an invasive LRR. Three hundred fifty-six patients had no prior or concurrent invasive disease in either breast; 3 (0.84%) developed distant metastases. One patient developed a recurrence within two years of mastectomy, the remainder recurred 2.3 to 11.5 years after mastectomy. Conclusions: Recurrence after mastectomy for pure DCIS is rare. Although recurrences are uncommon, long-term follow up should be offered to patients treated with mastectomy for DCIS.

	Locoregional Recurrence	Distant Recurrence
Number of recurrences	5	3
Median time to recurrence, months (range)	45 (21-107)	118 (72-138)
Recurrence site		
	4 chest wall	3 lung/pleura
	1 axilla	2 concurrent bone
Margin status		
<2 mm	1	0
≥2 mm	2	2
Unknown	2	1
Grade		
Low	1	0
Intermediate	0	1
High	2	2
Unknown	2	0
Estrogen receptor status		
Positive	2	1
Negative	0	0
Unknown	3	2
Progesterone receptor status		
Positive	1	0
Negative	1	1
Unknown	3	2
Sentinel lymph node biopsy		
Micrometastases	0	0
Negative	3	3
Unknown	2	0

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Prognostic Value of Lymph Node Ratio in Node-positive Breast Cancer

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Background Axillary lymph node involvement and status are among the most important prognostic factors in breast cancer. Nodal status of breast cancer is based on the number of involved lymph nodes (LNs) and is staged with the current TNM classification. Since axillary dissection in sentinel node positive patients is not always performed nowadays, information on lymph node ratio (LNR) is less often know. In this study, we assessed the value of the LNR, defined as the ratio of LNs to the total number of removed LNs. Methods Using data from the Dutch Cancer Registry, all women diagnosed with node-positive breast cancer between 1999 and 2005 were identified. The prognostic value of LNRs was calculated by Cox regression analysis. Kaplan-Meier survival analysis was performed with groups compared by the log-rank test. Variables analysed for impact on disease-specific survival rates included the number of positive nodes, pN classification and the calculated LNR. Based on maximum likelihood, we identified cutoff points classifying women into low-, intermediate- and high risk LNR groups. Results From 69,566 patients a complete LN evaluation could be performed: 41,258 patients (59%) were LN- and 28,308 (41%) were LN+. 19,237 patients (68%) had 1 to 3 positive LNs, 6,096 (21%) had 4 to 9 positive LNs, and 2,975 (11%) had 10 or more positive LNs. The median number of positive LNs was 3 and median LNR was 0.21. LN status was associated with 5-year overall survival (OS) (88% and 78% for LN- and LN+ groups respectively, $p < 0.01$). LNR was also associated with OS. Optimal cutoff points classified node-positive patients into low- (≤0,18), intermediate- (>0,18 and ≤0,43) and high- (>0,43) risk groups, corresponding to 5-year disease-specific survival rates of 84%, 78% and 59%, and adjusted mortality risks of 1 (reference), 1.32 (95% CI, 1.13-1.53) and 1.97 (95% CI, 1.62-2.39), respectively. Conclusion Our data show that LNR has an important prognostic value in assessing breast cancer survival, which is more accurate than pN classification.

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Intracystic Papillary Carcinoma of the Breast: A Limited Role for Axillary Sampling C.G. Chiu,[1]* A.M. Leung,[1] D.M. Hari,[1] M. Sim,[1] A.J. Bilchik.[2] *1. Surgery, John Wayne Cancer Institute, Santa Monica, CA; 2. David Geffen School of Medicine at University of California, Los Angeles, CA.*

Introduction: Intracystic (encapsulated) papillary carcinoma (IPC) is a rare breast tumor and the optimal management of the axilla is unknown. The objective is to evaluate the incidence of axillary nodal metastasis in IPC. Methods: The Surveillance, Epidemiology and End Results (SEER) database was queried for cases of breast IPC diagnosed between 1983 and 2008. Individuals with another associated breast carcinoma were excluded. Clinicopathologic and treatment data were abstracted for each case. Results: A total of 1253 cases of breast IPC were identified (652 with invasion and 601 pure). There were significantly more pure IPCs diagnosed in the latter half of the study period ($p<0.001$) and 93% were Estrogen Receptor (ER) positive compared with 87% in the invasive group ($p=0.018$). Only 9.7% of patients with invasive IPC had nodal metastases and none with pure IPC. Conclusions: Breast IPC tumors are a rare variant of breast cancer. This report which represents the largest series to date suggests that the biological behaviour is different with almost all patients expressing ER positivity and few with nodal metastases. Careful pathological evaluation is essential because of a very limited role for axillary sampling.

	Invasive IPC (n=652)	Pure IPC (n=601)	p-value
Surgery: Breast			
lumpectomy alone	211 (33.2)	261 (44.2)	<0.001
lumpectomy and radiation	198 (31.2)	197 (33.3)	
mastectomy	210 (33.1)	122 (20.6)	
no treatment	16 (2.5)	11 (1.8)	
Surgery: Axilla			
nodal surgery	367 (56.5)	161 (26.8)	<0.001
no nodal surgery	283 (43.5)	440 (73.2)	
Axillary Lymph Node Status			
positive	35 (9.7)	0 (0.0)	<0.001
negative	326 (90.3)	145 (100.0)	

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Adjuvant Radiation Therapy and Survival for Pure Tubular Breast Carcinoma - Experience from the SEER Database B. Li,[1]* M. Chen,[1] D. Nori,[1] S.L. Chen.[2] *1. Radiation Oncology, Weill Cornell Medical College, Flushing, NY; 2. University of California Davis Cancer Center, Sacramento, CA.*

Purpose: Pure tubular carcinoma of the breast (PTCB) represents a distinct subtype of invasive ductal carcinoma (IDC) which is generally thought to be associated with better prognosis than even low grade IDC. There has been controversy as to the role of adjuvant radiation (RT) in this population. We hypothesized that adjuvant RT would demonstrate a survival improvement. Materials and Methods: We queried the Surveillance, Epidemiology and End Results Database for the years 1992-2007 to identify patients with pure tubular carcinomas of the breast. Patient demographics, tumor characteristics, and surgical and RT treatments were collected. Survival analysis was performed using the Kaplan-Meier method for univariate comparisons and Cox proportionate hazards modeling for multivariate comparisons, stratifying on the basis of age with a cutoff age of 65. Results: 6,465 patients were identified. 3624 (56.1%) underwent lumpectomy with RT (LUMP+RT), 1525 (23.6%) underwent lumpectomy alone (LUMP), 1266 (19.6%) received mastectomy alone (MAST), and 50 (0.8%) underwent mastectomy and RT (MAST+RT). When comparing the LUMP+RT and LUMP groups directly, those receiving adjuvant RT tended to be younger and were less likely to be hormone receptor positive. Overall survival is 95% for LUMP+RT and 90% for LUMP at 5 years. For those 65 or under, the absolute overall survival benefit of LUMP+RT over LUMP was 1% at 5 years, and 3% at 10 years. On stratified multivariate analysis, adjuvant RT remained a significant predictor in both age groups ($p=0.003$ in age ≤ 65, and $p=0.04$ in age > 65). Other significant unfavorable factors were older age and higher T stage (age > 65 only). Conclusions: Since sufficiently powered large scale clinical trials are unlikely, we would recommend consideration for adjuvant radiation in PTBC patients age 65 or under, although consideration of the small absolute survival benefit is important. Adjuvant radiation can be omitted for patients older than 65.

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Outcome of Lobular Neoplasia with Surgical Excision or Observation M. Beaucaire,[1]* K. Zabicki,[2] K. Yao,[1] T. Czechura,[1] B. Martz,[1] R.A. Goldschmidt,[1] E. Barrera, Jr.,[1] D.P. Winchester,[1] D.J. Winchester.[1] *1. Surgery, NorthShore University HealthSystem, Evanston, IL; 2. Dana Farber Cancer Institute, Boston, MA.*

Background The management of lobular neoplasia (LN) diagnosed on core needle biopsy (CNB) remains controversial. This study evaluates the outcome of 200 patients with LN managed with surgical excision or observation. Methods A retrospective analysis was performed from 1997-2011, identifying 200 patients with a diagnosis of LN diagnosed on core needle biopsy. Pleomorphic LCIS was excluded. 126 were further evaluated by excisional biopsy. 74 patients were managed with observation. All pathology was independently reviewed. Logistic regression was used to determine associations between clinicopathologic variables and cancer on excision. Results. The mean age was 55 years (range 37-84). 39 (20%) had a family history of breast cancer. 104 (52%) were postmenopausal. 86 (68%) with atypical lobular hyperplasia (ALH) had excision; 13 (15%) were upstaged to cancer. 29 of 58 (50%) with lobular carcinoma in situ (LCIS) had excision; 10 (34%) were upstaged. 11 of 15 (73%) with both ALH and LCIS had excision; none had cancer. Of the 23 (18%) upstaged to cancer, 6 (26%) had IDC, 8 (35%) had ILC, 1 (4%) had IDC and ILC, and 8 (35%) had DCIS. Mean tumor size was 1.0 cm (range 0.2-2.6 cm). Stage distribution: 9 stage 0, 11 stage I, 2 stage II, and 1 stage III. 15 (65%) were estrogen receptor positive. Age, hormone replacement therapy use, menopausal status, mammographic density, previous breast biopsy, and family history of breast cancer were not significant predictors of cancer upon excision. Of the 74 patients who did not undergo excision (mean follow 72, range 0-157 months), one was diagnosed with ILC. There was no significant difference in age between patients treated with excision or observation. Conclusions Excision of LN after CNB leads to an 18% upstaging to cancer with a significant proportion of invasive cancers (61%). Observation of LN diagnosed by CNB is associated with a low rate of subsequent cancer, suggesting that the time interval required for clinical manifestations of LN associated cancer is greater than 6 years. Until clear predictive variables are established to select subgroups for observation or excision, surgical excision should be performed for all patients with LN diagnosed by CNB.

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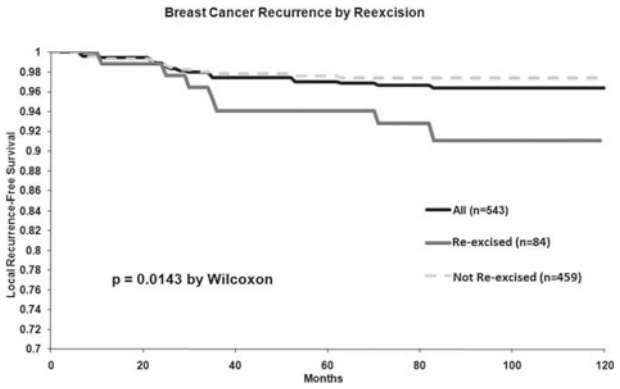
Low Local Recurrence Rates Despite Minimal Use of Re-excision following Breast Conservation Surgery B.J. Adams,* C.E. Stevenson, H.D. Bear. *Surgery, Virginia Commonwealth University, Richmond, VA.*

Introduction: Breast conservation surgery (BCS) results in survival equal to mastectomy for early stage breast cancer. Ipsilateral breast tumor recurrence (IBTR) after BCS is thought to be related to margin status. At our institution, re-excision is generally performed only if tumor cells are at the inked margin or if there is extensive disease close to multiple margins. The purpose of this study was to determine the rates of re-excision and local recurrence among BCS patients using this "conservative" re-excision policy. Methods: We performed an IRB-approved retrospective analysis of BCS patients between January 1, 2001 and June 30, 2005. We identified patients who had a second breast excision procedure within 8 weeks of the first, and those patients who had an IBTR with follow-up through March 2011. Clinical and pathologic features of all patients' tumors and re-excision specimens were reviewed. Results: We identified 543 patients who underwent BCS for a known diagnosis of breast cancer. 84 patients (15.5%) underwent a re-excision to address margin status. Overall, the crude IBTR was 3.5%, and the 5- year local recurrence-free survival of the re-excised group was 94% compared to 97.6% in the non-re-excised group ($p=0.0143$, Figure 1). Of the 84 patients who underwent re-excision for positive or multifocal close margins, 7 patients (8.3%) had an IBTR. In comparison, of the 459 patients who did

not undergo re-excision, only 12 patients (2.6%) had an IBTR (p=0.0175). Discussion: Our rate of re-excision is quite low compared to other recently reported series, despite not using intraoperative pathology. This results from a policy that defines "no tumor on ink" as an adequate margin for BCS and the use of selective irradiation boosts based on margin width carefully assessed by our pathologists. With this approach, our local recurrence rate compares favorably with those seen in other studies. Therefore, our conservative policy minimizes the need for additional surgical procedures and does not significantly compromise local control after BCS. Higher IBTR after re-excision likely reflects tumor biology of those with positive margins at the first operation.



10 year local recurrence-free survival of breast conservation surgery patients broken down by re-excised (red line) or not re-excised (green line).

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Rural and Urban Disparities in the Evolution of Sentinel Lymph Node Utilization in Breast Cancer A.K. Arrington,* J. Kim, L. Kruper, S.L. Chen. *City of Hope National Medical Center, Duarte, CA.*

Background: Since its introduction in 1994 for breast cancer, sentinel lymph node biopsy (SLNB) has become the preferred method for axillary nodal staging. We examined SLNB utilization in urban versus rural settings as this procedure was adopted. We hypothesized that SLNB rates in urban centers quickly increased prior to 2000, while the technology shift and acceptance of SLNB was slower in rural centers. Methods: The Surveillance Epidemiology and End Results registry was used to identify patients with invasive ductal or lobular breast cancer from 1998 to 2004. Patients were excluded if they had evidence of distant metastatic disease or T4 tumors, did not undergo an operation directed at cure, or had incomplete staging data. Patients were evaluated by standard demographic, clinical, and pathological indices. Residential setting was divided into three groups based on population density: rural, intermediate population, and urban. Results: The overall rate of SLNB increased with time (from 13.3% in 1998 to 55.2% in 2004). The adoption of SLNB was slower in rural settings than in urban populations (p<0.001). By 2004, only urban areas were utilizing SLNB in more than 50% of potential cases. Overall, there was a two-year lag between the increases in SLNB utilization rates in these groups. There was a significant difference in SLNB rates according to tumor size, with lower T stage positively correlating with the likelihood of SLNB usage (63.7% v. 47.2% v. 32.8%) by 2004. Conclusion: Since 1998, the use of SLNB for breast cancer has slowly increased throughout the United States. Though widely accepted as the preferred staging method, the overall rate of SLNB remained relatively low in 2004, especially in more rural locations. While this may represent a more conservative approach as noted by the higher utilization in small tumors, the difference may be attributable to a shortage of experienced surgeons, lack of training, or lack of technological support at smaller institutions. The provision of continued training in emerging technologies for rural surgeons, such as SLNB, should remain a priority in continuing surgical education.

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Breast Conservation Surgery in the Medicare Patient: Will the American College of Surgeons Oncology Group Z0011 Trial Change the Pattern of Care? C.E. Loveland-Jones,[1]* K. Ruth,[3] E.R. Sigurdson,[2] B.L. Egleston,[3] M. Boraas,[2] R.J. Bleicher.[2] *1. Dept of Surgery, Temple University School of Medicine, Philadelphia, PA; 2. Dept of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 3. Dept of Biostatistics, Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Some patterns of care for breast conservation surgery (BCS) in the US have been explored. While lymphatic mapping/sentinel lymphadenectomy (LM/SL) is standard in BCS, timing of LM/SL vs axillary dissection (AD) in the BCS patient, with attention to the impact of ACOSOG Z0011, remains unknown. Methods: Surveillance Epidemiology and End Results data linked to Medicare insurance claims for 1999-2005 were reviewed for female patients having invasive nonmetastatic breast cancer and nodal staging on the same day as BCS. Results: Among 25,887 BCS patients, those having simultaneous LM/SL increased from 22.7% in 1999 to 83.8% in 2005 (trend p=0.0003). In contrast, ADs declined on the BCS date for LM/SL patients, from 66.7% in 1999 to 42.1% in 2005 (trend p<0.0001). For patients with T1/T2 primaries, this trend is similar (66.8% to 41.9%, p<0.0001). During this time, there were 3,280 (12.7%) T1/T2 LM/SL node-positive patients, of whom 2,098 (64.0%) underwent AD on their BCS date. Among those with 1-2 positive nodes and T1/T2 primaries (n=2,532), 1,519 (60.0%) underwent AD on the BCS date, most of whom would likely now be spared AD. Among all 3,280 node-positive T1/T2 patients, ACOSOG Z0011 would theoretically spare most of the 2,532 (77.2%) from AD. These patients had a median tumor size of 1.7 cm. Among those with T1/T2 primaries and >2 positive nodes (n=748), 579 (77.4%) underwent AD on their BCS date, many of whom would now wait for permanent section but still need AD at a later date (median primary size=2.1 cm, median nodes positive=5). Among these, 160 (27.6%) underwent breast re-excision or completion mastectomy on a later date anyway, suggesting that ACOSOG Z0011 may add a separate procedure to 419 (12.8%) node-positive T1/T2 patients. Conclusion: Most Medicare patients having BCS and LM/SL who are node-positive have AD on their BCS date. If prior claims are indicative of future impact, ACOSOG Z0011 will increase the number of BCS patients requiring additional surgery but decrease the number of patients requiring AD to a far greater extent. The cost and resource implications have yet to be determined.

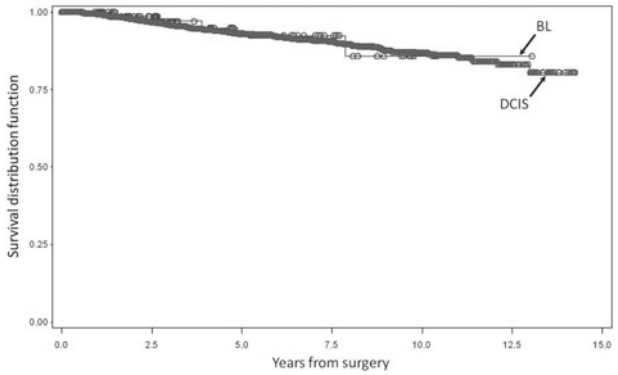
P66

Blurry Boundaries: 'Borderline' Lesions and DCIS of the Breast D.X. Choi,* S. Patil, A.A. Eaton, J. Goldberg, M. Morrow, K.J. Van Zee. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction. Ductal neoplasias of the breast span from atypical hyperplasia [ADH] to carcinoma in-situ [DCIS] to invasive carcinoma [INV]. The histology of 'borderline' lesions [BL], which have features in between ADH and DCIS, is well-described, but the clinical behavior is not. This report aims to determine the rate of ipsilateral breast tumor recurrence [IBTR] in patients undergoing breast-conservation [BCS] for BL. Methods. A prospective registry of patients treated with BCS for BL or DCIS from 1997-2010 was reviewed. BL and DCIS patients were compared. Patients subsequently diagnosed with DCIS or INV in the ipsilateral breast were considered to have IBTR. Patients were censored at last follow-up or death. Results. 2276 patients underwent BCS for BL (n=99) or DCIS (n=2177). Median follow-up was 37 months for BL (0.3-157) and 54 months for DCIS (0-171). For patients with BL, the median age was 51 years (25-80); 50 (51%) were pre-/peri-menopausal; 38 (38%) reported a family history of breast cancer; 89 (90%) presented radiologically; 25 (25%) had positive or close margins. 5 patients with BL (5%) had IBTR at 27, 33, 47, 60, and 96 months after surgical completion. 1 (1%) developed DCIS; 4 (4%) developed INV. All had negative margins; none received radiotherapy or endocrine therapy. 5- and 10-year IBTR rates were 8% and 14% respectively. Kaplan-Meier analysis [KM] failed to demonstrate differences in IBTR rates between BL, and low-, intermediate-, and high-grade DCIS, p=0.66. Because very few BL patients received radiotherapy (n=2, 2%), analyses were repeated for the BL and DCIS subsets that did not receive radiotherapy (n=96 and n=867, respectively). KM failed to demonstrate differences in IBTR rates: BL vs all DCIS, p=0.35 [Figure]; BL vs low- vs intermediate- vs high-grade DCIS, p=0.22. Conclusions. This clinical audit failed to demonstrate statistically-significant differences in IBTR between BL and DCIS, two adjacent entities on the continuum of ductal neoplasias of the breast. Indeed,

despite 'borderline' histology, 5- and 10-year IBTR rates of 8% and 14%, respectively, suggest that the risk of future carcinomas is not negligible, especially since most IBTRs were INV.

Kaplan-Meier Curve, comparing rates of ipsilateral breast tumor recurrence free survival in patients who did not undergo radiotherapy with 'borderline' lesions [BL] (n=96) and ductal carcinoma *in-situ* [DCIS] (n=867) of the breast. p=0.35.



P67

Mucinous Carcinoma of the Breast: The Mayo Clinic Experience over 20 Years J. Arun,* S.S. Shah, C. Reynolds, J.K. Brodt, J.C. Boughey. *Mayo Clinic, Rochester, MN.*

Introduction: Pure mucinous breast carcinoma (PMBC) is a rare subtype comprising 2% of breast carcinomas. Due to the rarity of PMBC, the literature contains case cohorts of 60-80 patients. This study aims to describe one of the largest reported case cohorts of PMBC. Methods: With IRB approval, we retrospectively analyzed all mucinous tumors from 1990 to 2010. All histologic slides were reviewed by two pathologists. PMBC was defined as 90% or greater tumor cells floating in mucin and low nuclear grade. Solid papillary, invasive micropapillary and DCIS with mucin extravasation were excluded. Records were reviewed for demographic data, operative intervention, adjuvant therapy, and outcomes. Results: Over 20 years, 134 women with PMBC were identified. The average age of these patients was 68 years (range 25-91). Forty-seven women (35%) underwent mastectomy, of which 4 received post-mastectomy radiation. Eighty-seven women (65%) underwent lumpectomy, of which 60 received adjuvant radiation. Mean tumor size was 1.47 cm (range 0.7-5.3 cm) with 79.1% T1, 19.4% T2, and 1.5% T3 tumors. Most tumors were grade I (84%) with 16% grade II, and no grade III. 82% were estrogen receptor positive. Initial axillary lymph node dissection (ALND) was performed in 33 patients (25%), sentinel lymph node (SLN) surgery in 64 patients (48%), SLN surgery with ALND in 14 patients (10%), and no nodal staging in 23 patients (17%). Overall 8 patients were node positive (7%). In the SLN group five cases were node positive, each with one positive SLN - 4 with micrometastases and 1 with a 4 mm macrometastasis. Four of these patients underwent completion ALND, with no additional positive nodes. In the ALND group 3 patients were node positive with 1, 4 and 9 positive lymph nodes. 8 patients received adjuvant chemotherapy and 52 patients received adjuvant endocrine therapy. With a mean follow-up of 53 months (range 0-226 months) seven patients (5%) have recurred, three with distant metastasis and four patients deceased from breast cancer (3%). Conclusion: Pure mucinous breast carcinoma presents at an early stage in an older population with a small primary tumor and is usually node negative with low mortality.

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Adherence to Anti-estrogen Therapy in Seniors with Breast Cancer: How Well Are We Doing? N. Trabulsi,[1]* K.E. Reidel,[2] N.E. Winslade,[2] J. Gregoire,[3] S. Meterissian,[1] M. Abrahamowicz,[2] R. Tamblyn,[2] N. Mayo,[2] A. Meguerditchian.[1] *1. General surgery, McGill University, Montreal, QC, Canada; 2. Departement of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada; 3. Department of Pharmacy, Laval University, Québec, QC, Canada.*

BACKGROUND: Nearly a third of breast cancers (BC) occur in women 65 and older. Anti-estrogen therapy (AET) significantly reduces BC recurrence and death in these patients, as they more often have hormone receptor positive tumors. However, studies suggest that adherence to AET in older women is a challenge. OBJECTIVE: To characterize AET adherence in seniors with BC and identify factors influencing it. METHODS: Cancer registry data and administrative claims for all non-metastatic BCs diagnosed in Quebec between 1998 and 2005 were accessed from the provincial health insurance program. Patients ≥ 65 who started AET (Tamoxifen, Anastrozole, Exemestane or Letrozole) and had 5 years of follow up were studied. Five-year medication possession ratio (MPR) was calculated and multivariate linear regression was used to assess the association between patient, disease, and physician characteristics and MPR. RESULTS: 4,715 women were included. Mean age was 72.9. 32.4% of patients had a Charlson comorbidity index 1-3. Stage distribution was: 6% in situ, 74% localized, and 20% regional disease. Mean MPR was 83.5% (SD 26.8%). 5-year MPR decreased with increasing age (p=0.015), ER visits (p=0.01) and hospitalizations not related to BC (p<0.01). Women with in-situ or localized disease had lower MPR than those with regional disease, (7.5% and 2.1% respectively, p<0.05). In comparison to women who received chemotherapy, those who were not considered for chemotherapy had 5% decrease in their MPR (p<0.01). Being on antidepressants at baseline decreased MPR by 3.7%, (p=0.03). In comparison to those who did not switch AET during the 5-year course, switching AET in the 3rd to 5th years increased the MPR by 7.4%, (p <0.01). Switching in the 1st or 2nd year did not have a significant impact on adherence. Women on Tamoxifen had 4.1% lower MPR than those on Aromatase Inhibitors, (p=0.018). Having a non-surgeon prescribe AET increased MPR by 2.7% (p<0.01). CONCLUSION: Most seniors with BC had high adherence to AET. Patients with more advanced age, less advanced disease and non-BC related health service use, and women treated with antidepressants were at higher risk of suboptimal adherence.

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The Significance of Lobular Carcinoma In Situ and Atypical Lobular Hyperplasia of the Breast J. Lewis,* D. Lee, P. Tartter. *St. Luke's-Roosevelt Hospital, New York, NY.*

Introduction: The significance of lobular neoplasia (LN) (lobular carcinoma in-situ [LCIS] and atypical lobular hyperplasia [ALH]) found at core needle biopsy of the breast remains uncertain. The reported association with malignancy ranges from 0 to 60% and there is a consistent risk of underestimating malignancy after the diagnosis of LN on core biopsy. The aim of this study is to determine if patients with a core biopsy result of LN need surgical excision. Methods: Patients were identified by searching the institutions pathology database for the terms "lobular carcinoma in-situ" and "atypical lobular hyperplasia" between the years of 1991- 2011. Excluded from this study were patients with core biopsy results of ductal carcinoma in-situ, atypical ductal hyperplasia, radial scar, or papilloma. Results: Lobular neoplasia was found at core needle biopsy in 224 patients and 71% (159) had subsequent surgical excision. The indications for core needle biopsy were mammographic findings of new calcifications in 58% (129), palpable mass in 0.5% (11), and architectural distortion, a new shadow or a new density in 0.3% (7). The indication was unknown for 77 patients. Final pathology of the surgically excised specimens confirmed LN in 85% (136): 53 of LCIS, 33 of ALH and 50 mixed LN. Fifteen percent (24) of the operated patients were found to have malignancy: 9 had ductal carcinoma in situ, 10 had invasive lobular carcinoma and 7 had invasive ductal carcinoma. Two patients with invasive cancer had lymphovascular invasion on sentinel lymph node biopsy, 11 had lymph nodes negative for invasion and 4 patients were not tested or the results were not available. Other benign pathologies were found in seventeen percent of patients: atypical ductal hyperplasia (20), papilloma (10), radial scar (6) and phyllodes tumor (1). Conclusion: This is the largest series of surgical excisional pathology following LN on core needle biopsy ever reported. The likelihood of finding malignancy at surgical excision after core needle biopsy showing LCIS or ALH was fifteen percent. Patients with the diagnosis of LN on needle biopsy should be considered for surgical excision.

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Radiation Therapy after Breast Conserving Surgery: When are We Missing the Mark? K.E. Reidel,[2] N. Trabulsi,[1]* S.H. Meterissian,[1] R. Tamblyn,[2] N. Mayo,[2] A.N. Meguerditchian.[1] *1. General surgery, McGill University, Montreal, QC, Canada; 2. Departement of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.*

INTRODUCTION: Postoperative radiation therapy (RT) after breast conserving surgery (BCS) represents the standard of care for local control of breast

cancer (BC). Despite wide dissemination of clinical guidelines, variations in practice persist. OBJECTIVE: To identify patient, disease, and physician characteristics that predict lack of a consultation for RT after BCS. METHODS: Cancer registry data and administrative claims for all BCs diagnosed in Quebec between 1998 and 2005 were accessed from the provincial health insurance program. Receipt of a consultation for RT within 1 year of BC diagnosis was measured in adult women with invasive, non-metastatic BC treated with BCS. Multivariate logistic regression was used to assess the association between patient, disease, and physician characteristics and having an RT consult. RESULTS: 27,483 women were included. Mean age was 59.5 years, 76.5% had no comorbidities, and 27.6% had stage III BC. Overall, 90.1% of women were considered for RT within 1 year of diagnosis. At multivariate analysis, patients at age extremes were less likely to get RT as compared to women 50-69: those 30-49, 70-79 and 80+ had odds ratios (OR) of 0.82 (CI 0.73-0.93), 0.54 (CI 0.48-0.61), and 0.11 (CI 0.09-0.12) respectively. Women with any ER visit and women with a hospitalization (unrelated to BC) had 15% and 17% lower odds of having an RT consult, respectively (CIs 0.76-0.94 and 0.71-0.97). In patients with node positive disease, receiving a consultation for chemotherapy within 4 months of BCS increased the likelihood of also being considered for RT within 1 year (OR 1.54, CI 1.19-2.00). Interestingly, in patients with localized disease, this association was even stronger (OR 2.28, CI 1.96-2.65). Physician BCS volume in the year prior to patient diagnosis increased the chance of their patient receiving an RT consult by 7% for every 10 more BCS performed (CI 1.03-1.10). CONCLUSION: Patient age, use of non BC-related health services and physician volume of BCS in the management of BC predicts use of RT. Guideline deviations in other aspects of BC management (such as chemotherapy) also predict variations in RT use.

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Association of Marital Status and Breast Cancer Outcome: A Population-based Study K.A. Caprio,* A.B. Chagpar, D. Lannin. *Surgery, Yale University School of Medicine, New Haven, CT.*

Introduction: Social support is known to positively impact health outcomes. Marital status has been studied as a prognostic factor in cancers such as colon and pancreas, but there are few studies in the breast cancer literature. **Methods:** The SEER database was queried regarding marital status and breast cancer stage and survival for patients diagnosed between 1988 and 2008. Early stage was defined as AJCC stage 0 or 1. The life table method was used to determine 5 year breast cancer specific survival. Women who were married at the time of diagnosis (including common law) were compared to women who were single, separated, divorced or widowed. **Results:** A total of 766,720 cases were available with information on marital status, stage and survival. Marriage was strongly associated with earlier stage of diagnosis and better 5 year survival. The effect was similar regardless of race/ethnicity, age at diagnosis, gender, or year of diagnosis ($p<0.001$ for all comparisons). Over the 20 year period, survival steadily increased, but the difference by marriage persisted. Interestingly, men with breast cancer seemed to benefit from marriage similarly to women. **Conclusion:** The social support provided by marriage benefits breast cancer patients to a similar extent as many adjuvant chemotherapy or radiation regimens. Further study is needed to understand the mechanisms of this so the benefit might be extended to non-married individuals.

	% Early Stage (AJCC 0-1)*		5-Year Breast Cancer Specific Survival (%)*	
	Married	Not Married	Married	Not Married
Sex				
Female	60	55	83	77
Male	45	36	77	66
Race				
White	61	57	83	78
Black	50	46	73	68
Hispanic	50	47	76	73
Asian	60	57	85	81
Age				
Under 50	54	49	81	76
50 - 65	62	56	84	79
Over 65	65	58	83	76
Year of Dx				
1988-1992	56	52	70	66
1993-1997	60	55	78	72
1998-2002	60	56	87	81
2003-2008	61	56	92	87

*** p < 0.001 for all comparisons between married and not married**

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Molecular Drivers of Breast Tumor Differentiation H. Patney,[1]* R.E. Ellsworth,[2] C.D. Shriver.[3] *1. Windber Research Institute, Windber, PA; 2. Henry M. Jackson Foundation, Windber, PA; 3. Walter Reed National Naval Medical Center, Bethesda, MD.*

Background: Histological grade classifies breast carcinomas into low- (G1), intermediate, and high-grade (G3). Both developmental pathways for high-grade disease including linear models, as well as models that depict G1 and G3 carcinomas as distinct molecular diseases remain controversial. We utilized global SNP arrays to measure copy number changes and LOH at high resolution to determine the evolutionary relationship between low- and high-grade tumors. Methods: The Clinical Breast Care Project database was queried to identify all G1 and G3 tumors with frozen tumor specimens available. Specimens (49 G1 and 77 G3) were subjected to laser microdissection and hybridized to the GeneChip Human Mapping 250K Sty arrays (Affymetrix). Copy number and LOH analysis were performed using Partek Genomics Suite segmentation analysis. Results: The most common alteration in both groups was gain of chromosome 1q (71% G1 and 69% G3). G1 tumors also had frequent loss of 16q (90%). G3 tumors acquired frequent gain of 8q and loss of 8p, 15q and 17p. Loss of chromosome 16q and gain of chromosome 8q were significantly higher ($P<0.00001$) in G1 and G3 tumors, respectively. The leading type of alteration of chromosome 16q in G1 tumors (65%) was loss of the entire arm; in G3 tumors, only 12% had complete loss, and 10% had no alteration. The majority of G3, however, had complex patterns of change including small (<1 Mb) deletions or amplifications scattered across 16q and complex patterns of alternating deletions and amplifications. LOH was not found in diploid or amplified regions. Conclusions: Gain of chromosome 1q is common in low- and high-grade tumors and may be an early event in tumorigenesis. G3 tumors did not show frequent loss of chromosome 16q, nor was frequent LOH detected in copy-neutral or amplified regions, suggesting that the complex patterns of gain and loss of chromosome 16q in G3 tumors are not the result of segmental gains subsequent to large-scale loss of 16q. Together, these data suggest that G3 tumors do not evolve from a well-differentiated precursor, but rather the development of G1 tumors is driven by loss of 16q, while G3 tumors are driven by more complex changes.

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Minimally Invasive Staging of the Axilla in Breast Cancer using Axillary Ultrasound, Fine Needle Aspiration Biopsy, and Real-Time RT-PCR J.A. Margenthaler,* C.M. Appleton, T.P. Fleming, M. Sturmoski, F. Gao, W.E. Gillanders. *Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

INTRODUCTION: We investigated the feasibility of axillary ultrasound (AUS), fine needle aspiration biopsy (FNAB), and real-time reverse transcription polymerase chain reaction (RT-PCR) to accurately stage the axilla in patients with clinically node-negative breast cancer. METHODS: Eighty patients were enrolled in a prospective study. Patients underwent AUS to evaluate lymph node morphology as either "normal" or "suspicious" by standard criteria. Patients with "normal" AUS underwent sentinel lymph node biopsy (SLNB) with FNAB intraoperatively. Patients with "suspicious" AUS underwent AUS-guided FNAB. FNAB specimens were analyzed by multimarker, real-time RT-PCR and compared to final pathology. RESULTS: In patients with a "normal" AUS (n=40), 34 were node-negative on final pathology, while 6 were node-positive. All 6 with node-positive disease had a positive marker profile. Of 34 patients with node-negative disease, 31 (91%) had a negative marker profile, while 3 (9%) had a positive marker profile. In patients with a "suspicious" AUS (n=40), 28 (70%) had positive cytopathology and histopathology. Twenty-three of 28 also had a positive marker profile, while 5 patients had a negative marker profile. Twelve of 40 patients with "suspicious" AUS (30%) had negative cytopathology. Five were node-positive on final pathology; 4 had a positive marker profile and 1 had a negative marker profile. Seven patients were node-negative on final pathology; 2 had a positive marker profile and 5 had a negative marker profile. Mean size of lymph node metastasis detected by the panel was 7.2 mm (range 3 mm – 1.7 cm). A positive marker profile was associated with traditional indicators of prognosis, including histologic grade, biomarker status, and tumor size ($p<0.05$ for each). The sensitivity and specificity of AUS, FNAB, and RT-PCR in predicting the pathologic status of the axilla was 85% and 88%, respectively. CONCLUSION: This is the first report to demonstrate that real-time RT-PCR analysis of FNAB specimens is feasible in predicting

the final lymph node status in patients with clinically node-negative breast cancer.

P74

Biological Features of Multifocal Breast Cancer B. Chikman, D. Zaid, R. Lavy,* J. Sandbank, A. Halevy. *Assaf Harofeh Medical center, Tel Aviv, Israel.*

Background Approximately 10% of the women with breast cancer have multifocal tumors. The clinical significance of few simultaneous tumors is controversial. The American Joint Committee on Cancer (AJCC) recommends to stage multifocal tumors according to the diameter of the largest tumor focus and lymph node status. Some studies demonstrated that aggregate tumor size is a more accurate predictor of axillary lymph node involvement and long-term outcome than the largest tumor size. We propose that multifocal breast cancer differ from unifocal by its biological features. Materials and methods. Patients with multifocal breast cancer were compared to a control group that was selected randomly from our computerized database. The study group included 212 patients with multiple tumors in the ipsilateral breast and a control group of 684 patients with unifocal disease. Results: Infiltrating lobular carcinoma and mixed (infiltrating lobular and infiltrating duct) carcinoma were more frequently associated with multifocal tumors compared to unifocal breast cancer (22.6% versus 9.5%) ($p<0.0001$). In comparison with the group of patients with unifocal breast cancer patients with multifocal disease were more common to have Her2-positive tumors (19.6% versus 11.2%, $p=0.019$) and less common to have triple-negative breast cancer (4.5% versus 13.3%)($p=0.01$). Multifocal breast cancer is found more frequently in association with axillary lymph node metastases (52.0% versus 37.1%, correspondently, $p=0.0002$) Tumor size (the largest in the multifocal group) was not statistically different between the two groups (mean size 2.2 cm). The differences in the rate of axillary lymph node metastases was not translated into differences in disease-free or overall survival. Conclusion: Biological patterns of multifocal breast cancer differ from unifocal, and that may explain the similar outcome in the two groups despite the extremely high rate of axillary lymph node metastases in the multifocal group.

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Validation of ACOSOG Z0011: Axillary Dissection is not Required for Positive Sentinel Lymph Nodes in Early Stage Breast Cancer K.E. Calhoun,[1]* S.H. Javid,[1] G.N. Mann,[1] D.R. Byrd,[1] K.H. Allison,[2] B.O. Anderson.[1] *1. University of Washington- Department of Surgery, Seattle, WA; 2. University of Washington- Department of Pathology, Seattle, WA.*

INTRODUCTION: The ACOSOG Z0011 trial challenges whether completion axillary node dissection (cALND) is required in breast conservation therapy patients when positive axillary sentinel nodes (SLNs) are identified in early breast cancer (BC). We examined if implementing the Z0011 protocol would have impacted pathologic staging or disease control in our patient population. METHODS: With IRB-approval, we identified all SLN biopsy BC patients treated from 2003 to 2009. Records of Z0011-eligible patients (1 or 2 N1mi/N1 positive SLNs, T1/T2 tumors, whole breast radiation) were reviewed. Age, primary tumor and SLN pathology features, final axillary management, staging and follow-up (f/u) status were determined. RESULTS: There were 62/206 (30%) SLN positive patients deemed Z0011-eligible, including 24 N1mi and 38 N1 positive SLNs. Mean age was 56.8 years (range 32-84). The average primary tumor size was 1.9 cm, with 27 T2 and 35 T1 lesions. Most were invasive ductal (84%), grade 2 (55%), ER/PR positive (94% and 89%), HER-2/neu negative (95%) tumors. Fifty-three patients had one and 9 patients had two positive SLNs. Overall, 46/62 (74%) underwent cALND (35/38 (92%) N1 v. 11/24 (46%) N1mi patients). While 14 (23%) had additional positive axillary nodes (12 N1 v. 2 N1mi), only 6 (10%) upstaged [pN1 to pN2], all initially N1. In total, 89% patients received chemotherapy, with A/T containing regimens more common than CMF with higher nodal burden (Table). At median 60.5 months (range 24-101), 3 patients (5%) have experienced disease failure, including one who upstaged to N2. One N1mi patient (cALND declined) developed stage 4 disease (bone) in spite of CMF. Despite cALND and AC/T, two N1 patients died of disease. There have been no locoregional recurrences regardless of whether cALND was performed. DISCUSSION: Our results confirm that Z0011 management is safe for breast conservation candidates with early stage disease. Limited upstaging, no loco-regional recurrences and excellent disease control all argue against mandatory cALND for Z0011–eligible patients. Only if upstaging would cause a significant change in adjuvant therapy is cALND warranted.

Adjuvant Systemic Treatment

	No Therapy	Endocrine Therapy Only	Chemotherapy
N1mi- no cALND (n=13)	1	4	Total- 8 CMF- 5 AC/T- 2 T/C- 1
N1mi- yes ALND (n=11)	0	1	Total- 10 CMF- 6 AC/T- 1 N/S- 3
N1- No cALND (n=3)	0	0	Total- 3 CMF- 1 AC/T- 1 T/C- 1
N1- yes cALND (n=35)	0	1	Total-34 CMF- 16 AC/T- 11 TC/H- 4 N/S- 3
Positive non-SLNs (n=14)	0	1	Total-13 CMF- 4 AC/T- 5 T/C- 2 N/S- 2
N1 to N2 upstaged (n=6)	0	0	Total-6 CMF- 1 AC/T- 2 T/C- 2 N/S- 1
Glossary: CMF- Cytoxan, Methotrexate, Fluorouracil	Glossary: AC/T- Adriamycin Cytoxan Taxol/Taxotere	Glossary: T/C- Taxol/Taxotere Cytoxan	Glossary: N/S- Not specified

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Excising Additional Tumor Cavity Margins at Initial Breast-conserving Surgery for Cancer Reduces the Need for Re-excision: A Report of a Randomized Prospective Study J. Linebarger,[1] S.G. Gabram,[1] H.L. Bumpers,[2] J. Okoli,[2] V. Brown,[1] B. Burns,[3] M. Mosunjac,[3] M. Rizzo.[1]* *1. Surgery, Emory University, Atlanta, GA; 2. Morehouse School of Medicine, Atlanta, GA; 3. Emory University Department of Pathology and Laboratory Medicine, Atlanta, United States, Georgia.*

Introduction: Margin status is an important prognostic factor for local recurrence after breast-conserving surgery (BCS) for breast cancer. We have previously shown in a retrospective study that taking additional tumor cavity margins at the time of initial BCS for infiltrating ductal carcinoma (IDC) reduces the re-operation rate with cosmetically acceptable results. The aim of this study is to report our results of a prospective randomized trail comparing BCS vs. BCS with resection of 5 additional margins (BCS+M). Methods: Female patients diagnosed at a single institution with Stage 0- IIIA breast cancer from November, 2009 to September, 2011 and eligible for BCS were randomized to BCS or BCS+M. Tumor margins were classified as negative (>2 mm for DCIS; >1 mm for IDC) or positive (≤2 mm for DCIS; ≤1 mm for IDC). Tumor histology, margin status, and re-operation rate were recorded. Data were analyzed using Fisher's exact test, and statistical significance was set at a p-value less than 0.05. Results: We randomized 71 patients (69 African American, 94%) with a mean age of 60.2 years (range 38.6-80.8). Thirty-five underwent BCS and 36 had BCS+M. Overall, 18 (25%) patients had positive margins: 14 (78%) who had BCS and 4 (22%) who had BCS+M ($p=0.003$). Seventeen of the 18 patients with positive margins had a component of DCIS on specimen pathology. Regardless of operative approach, patients with a component of DCIS had a higher rate of positive margins ($p=0.003$). All patients with positive margins were offered re-excision: 8 had tumor margin re-excision(s) and achieved negative margins, 6 had mastectomy, and 4 declined additional surgery (Table 1). Conclusions: Resection of 5 additional margins at the time of initial BCS for breast cancer is associated with a lower rate of positive margins and a higher rate of one step surgery that has been identified as a surgical quality measure of breast cancer care. DCIS, alone or in association with IDC, is a risk factor for positive margins.

Management of patients with positive margins

Number of Re-excisions	BCS (n=14)		BCS+M (n=4)	
	Mastectomy (n=5)	Margins Re-excision (n=9)	Mastectomy (n=1)	Margins Re-excision (n=3)
0	3*	4**	1*	-
1	1*	4	-	2
2	-	1	-	1
3	1*	-	-	-

BCS= Breast Conserving Surgery
BCS+M= Breast Conserving Surgery + 5 margins
* Number of re-excision prior to mastectomy
**Four patients refused additional surgery

P77

A Cost Analysis of MRI Utilization in Invasive Lobular Carcinoma
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Introduction: Breast MRI is well known to impact surgical management, particularly with lobular histology. There has been little discussion of whether the utilization of preoperative breast MRI impacts the total cost of care. The intent of this study was to evaluate if MRI use in women with invasive lobular carcinoma (ILC) resulted in significant changes to cost of care. Methods: Between 2007-2011, women with ILC undergoing up front surgery were recruited to a prospective registry study of breast MRI. Women meeting the same inclusion criteria, but without breast MRI, were retrospectively identified for comparison. Total cost of care was evaluated from the time of presentation to the date of final oncologic surgery or definitive reconstruction. Non-parametric bootstrapping was used to compare the unadjusted cost differences between groups. Results: Fifty-one patients had preoperative MRI, 60 patients did not. Women in the MRI group were younger (median age 55 vs 64 yrs, p=0.011). Method of diagnostic biopsy, clinical stage and pathologic stage were similar in the two groups. In the MRI cohort, 17 women (33%) had a second look US and 15 women (29%) had additional image guided biopsy. Median time from presentation to surgery was 29 days in the MRI group vs. 28 days in the non-MRI group. Thirty-six (71%) patients in the MRI group had mastectomy vs. 39 (65%) in the non-MRI group (p=0.53). Twelve (24%) patients had contralateral prophylactic mastectomy (CPM) in the MRI group vs. 9 (15%) in the non-MRI group (p=0.26). Women in the MRI arm were more likely to undergo reconstruction following mastectomy (61% vs. 39%, p=0.05). Mean total cost per patient in the MRI group was $28,927 (range: $11,555 to $71,656) and the non-MRI group was $23,694 (range: $10,375 to $53,218) (p<0.001). Excluding the cost of MRI, the mean total increased cost in this group was $4,595. Conclusion: In our series of patients with ILC, MRI did not delay surgical intervention or impact index mastectomy or CPM rates, but did increase the total cost of care. This increase in cost of care is due in part to a significant number of additional diagnostic interventions required to resolve MRI detected abnormalities.

P78

Contralateral Prophylactic Mastectomy: Characteristics Influencing Utilization
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Contralateral prophylactic mastectomy (CPM) rate have increased over the past decade. Patients in the southeast are less likely than those in other regions to undergo breast conservation therapy (BCT). Therefore, we examined characteristics related to patient, tumor, and surgeon in relation to surgery type in a large southeast regional medical center. Retrospective review of a prospectively maintained database of all patients who underwent surgical treatment for breast cancer between 2000 and 2009 was performed. Multivariate logistic regression models were used to compare characteristics associated with BCT and CPM. Exclusion criteria included unilateral mastectomy (n=761), bilateral disease, stage IV disease, and incomplete records. Of 1826 patients, 806 underwent BCT and 207 underwent CPM. Patients who underwent CPM were younger (52.9 versus 58.9; p<0.0001). Patients who never married were 82% more likely to undergo CPM than married patients (p<0.05). Obese patients were 72% more likely than those of normal weight to undergo CPM (p<0.05). In contrast, patient employed in a health care field and a family history of cancer were not associated with surgery type. Patients with moderately or poorly differentiated tumors were twice as likely to undergo CPM, and those with lobular carcinoma were four times more likely (both p<0.05). A small increase of CPM was noted in those who received an MRI, but this was not statistically significant. Patients under the care of surgeons with greater than 10 years experience were half as likely to undergo CPM, and patients of non-specialized surgeons were 64% less likely to undergo CPM (p<0.05). Multiple factors may be associated with the decision to pursue BCT vs. CPM. Study findings, particularly those related to surgeon specialty and experience, suggest the need to further understand the factors related to surgeon influences on patients' treatment choice. We plan to survey this cohort of patients to further determine psychosocial factors and patient satisfaction in regard to their surgical decision.

Table 1: Patient, Tumor, and Surgeon Characteristics Associated With Increase Rate of CPM.

Variable	OR	95% CI
Patient Age (continuous)	0.970	0.953-0.987
Patient Never Married (vs married)	2.066	1.51-3.706
Patient Obese (vs normal weight)	1.717	1.040-2.833
Tumor Grade Moderately Differentiated (vs well differentiated)	1.885	1.013-3.505
Tumor Grade Poorly Differentiated (vs well differentiated)	2.070	1.086-3.947
Tumor Morphology Lobular Carcinoma (vs Infiltrating Ductal Carcinoma)	4.167	2.168-8.007
Surgeon Experience >10yrs (vs <10yrs)	0.475	0.276-0.791
Surgeon Subspecialty-trained (vs non-specialized surgeons)	0.333	0.182-0.609

P79

Outcome of Sentinel Node Biopsies after Neoadjuvant Chemotherapy in Clinically Node-negative Breast Cancer Patients: A Follow-up Study in 148 Patients in Single Institution
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[Introduction] Sentinel node biopsy (SNB) and elimination of axillary clearance (Ax) after neoadjuvant chemotherapy (NAC) are still controversial. However, clinically node-negative patients in both pre- and post-chemotherapy are considered to be safe indicated to SNB from the reports of low false negative rate. Therefore, we evaluated the oncologic outcome of 148 patients underwent SNB after NAC. [Patients and Methods] Four hundred and fifty one patients received NAC during January 2005 to December 2009 in our institute. We indicate SNB after NAC for clinically node-negative patients in both pre- and post-chemotherapy by ultrasonogram and CT scan. The RI and blue dye methods and intraoperative histological diagnoses using H&E frozen sections were performed. [Results] One hundred and forty-eight patients underwent SNBs after NAC. Identification rate was 99% (147/148). Twenty-eight patients underwent immediate Ax because of positive metastatic nodes proven by intraoperative frozen sections. One hundred and twenty cases were eliminated of Ax. False negative rate of frozen section diagnoses was 13% (4 cases). Sixty-nine percent of patients had positive metastatic nodes in SNs alone. Ipsilateral axillary recurrences occurred in two cases (1.7%) of elimination of Ax cases. One also had ipsilateral breast recurrence and the other also had lung metastases. On the other hand, ipsilateral axillary recurrences occurred in 8 cases (2.4%) of 331 Ax cases. [Conclusion] The eliminations of Ax from results of SNB were safe in the patients with clinically negative nodes in the both pre- and post-chemotherapy. For more accurate intraoperative diagnosis, the immunohistochemistry may be useful and necessary.

P80

Trends in Arm Swelling and Patient Worry for the Development of Lymphedema after Axillary Surgery for Breast Cancer
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Background: Lymphedema (LE) is a feared complication of breast cancer (BrCa) surgery. Existing literature however lacks prospective data on the pro-

gression of arm swelling and the onset of LE. Using our ongoing axillary surgery registry we sought to evaluate the trends in LE development, patient worry, and risk reduction behaviors. Methods: Between 12/08 and 6/10 we prospectively enrolled 120 women undergoing axillary surgery for BrCa. We assessed LE by upper extremity (UE) volume preoperatively and at 6 and 12 months postoperatively and considered LE to be present if >10% change from baseline existed relative to the contralateral UE. All patients completed a validated instrument evaluating LE worry and risk reducing behaviors. Associations between LE, worry, and behaviors were determined by Fisher's exact and Signed Rank tests. Results: In total, 53 (44%) women had axillary dissection (ALND) and 67 (56%) had sentinel node biopsy alone (SLNB). At 6mo, LE rates were similar between ALND and SLNB patients (6% vs 2%, p=0.22), however at 12mo significantly more women having ALND had LE (19% vs 3%, p=0.005). Strong evidence supported a relationship between the relative change in UE volume at 6 and 12mo (Kendall Tau coefficient 0.504, p<0.001). Interestingly of the 114 women whose relative volume change was 0-9% at 6mo, 25/114 (22%) had worsening UE swelling of whom 9/25(36%) progressed to LE at 12mo. Conversely, 19/114 (18%) had resolution of their relative UE volume change. Regardless of surgery, patient worry about LE persisted with 75% vs 76% ALND and 52 vs 49% SLNB patients citing worry at 6 and 12mo respectively (both p>0.45). Finally, ALND and SLNB patients followed a similar number of risk reducing behaviors (5 vs 4, p>0.34) at both 6 and 12mo. Conclusions: UE volumes fluctuate and a period of latency prior to the development of LE exists. Despite the low risk of LE after SLNB a large number of women worry about LE and the majority of all women practice risk reducing behaviors. Further study into the early UE volume changes is warranted to allay the fears of most women and better predict which women will progress to LE.

P81

Fine Needle Aspiration (FNA) has Value in the Detection of Image-negative Breast Cancers A. O'Connor,[1]* J. Jean-Gilles,[2] N. Patwardhan,[1] A. Larkin,[1] G. Whalen,[1] C. Owens,[2] R. Quinlan,[1] A. Fischer.[2]
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Background: Over the last decade there has been a decline in breast FNA. This is due in part is to concerns about lack of sensitivity of FNA, and the potential for equivocal cytologic diagnoses to inappropriately increase the rate of open biopsies. Many centers are trending towards ultrasound guided core needle biopsy, but 9-20% of breast cancers may not show a radiologic target for biopsy. This study tested the hypothesis that non-image guided FNA can be useful in detecting radiologically negative breast cancers. Methods: A retrospective review of all FNAs performed by an experienced breast surgeon, without on-site cytologic evaluation, for non-cystic lesions over a five year period in a university-based comprehensive breast cancer center with experienced cytopathologists was performed. Patient demographics, radiological reports, clinical examinations and pathology reports were reviewed. Results: Of 1532 FNA specimens, 1246 (82%) were Negative, 63 (4%) were Atypical (of which 41% proved to be carcinomas on follow-up biopsies), 18 (1%) were Suspicious for Malignancy, 129 (8%) were Positive for Malignancy, and the remaining 76 (5%) were Non-diagnostic. There were no false positive FNA diagnoses. Of the Positive and Suspicious for Malignancy lesions, 14 patients with cancer (10% of all cancers) had concurrent negative imaging studies and 10 had low suspicion on clinical exam. An additional 32 positive FNA samples were performed based on clinical suspicion alone before imaging studies had been performed; 6 of these 32 had subsequent negative imaging studies. Conclusions: When experienced clinicians and cytopathologists are available, FNA should be used in the evaluation of a patient referred for a questionable breast abnormality. In our cohort, 14 of 129 breast cancer patients (10%; 1.1% of all patients) could have had a delay in diagnosis due to the absence of a radiologic target for biopsy. Equivocal (Atypical and Suspicious) diagnoses were uncommon (5%) and appropriately required histologic evaluation. FNA is easily performed in an office setting, with minimal discomfort to the patients, and with rapid and accurate results

P82

Development of a Prediction Model for Treatment Response to Neoadjuvant Chemotherapy in Patients with Primary Breast Cancer Using a Decision-tree Algorithm M. Toi,[1]* M. Takada,[1] M. Sugimoto,[2] Y. Naito,[3] H. Bando,[4] H. Iwata,[5] K. Kuroi,[6] N. Masuda,[7] S. Ohno,[8] N. Sato,[9] M. Kondo,[10] H. Sasano,[11] T. Inamoto,[12] M. Tomita.[3]
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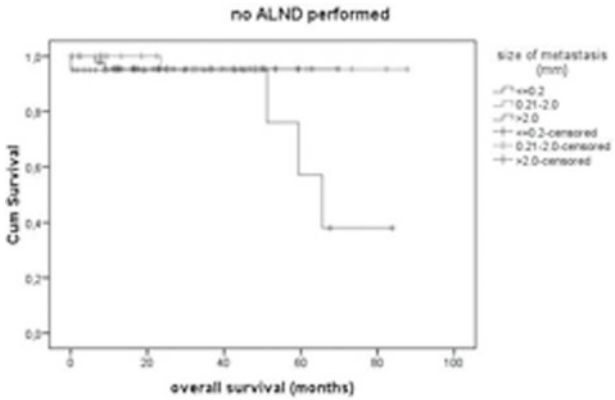
INTRODUCTION Neoadjuvant chemotherapy (NAC) has been increasingly indicated in patients with primary breast cancer. Although several clinical prediction models or genetic predictors for chemosensitivity have been reported, prediction of chemosensitivity is still difficult. The aim of this study was to develop an accurate clinical prediction model for pathological complete response (pCR) to NAC. METHODS Included were patients with invasive breast cancer who underwent NAC. 262 patients were included from a randomized clinical trial of NAC in which patients were treated with 4 courses of FEC followed by 4 course of docetaxel with or without capecitabine. 61 patients who were treated with the same chemotherapy protocol were also included. Clinicopathological information before starting treatment was collected from institutional databases retrospectively. Patients were divided into a modeling dataset (n=150) and a validation dataset (n=173) according to institution. We used an alternating decision tree (ADTree) algorithm for prediction model. pCR was defined as absence of residual invasive cancer cells in breast and axillary lymph nodes. RESULTS The model developed with 15 variables showed accuracy with the area under the receiver operating characteristics curve (AUC) values 0.766 (95%CI, 0.671 – 0.861) in the modeling dataset (cross-validation). Validation study using the independent dataset showed an AUC value of 0.787 (95%CI, 0.716 – 0.858). A false negative rate and a negative predictive value in the validation dataset were 7.7% and 95.9%, respectively. When clinical treatment response after FEC treatment was added to the model, the accuracy was improved from an AUC value of 0.787 to 0.820. CONCLUSIONS Our model was based on the data with a currently used treatment regimen. Although our model requires more variables compared to the previous models, our model showed a high accuracy in the validation study using an independent dataset.

P83

Is SLN Biopsy Alone a Therapeutic Tool in Breast Cancer? R.F. Van la Parra,[1]* S.J. Mol,[2] W.K. De Roos,[1] A.H. Mulder,[3] M.F. Ernst,[2] K. Bosscha.[2] *1. Surgery, Gelderse Vallei Hospital, Ede, Netherlands; 2. Jeroen Bosch Hospital, 's Hertogenbosch, Netherlands; 3. Rijnstate Hospital, Arnhem, Netherlands.*

Introduction: In international and national guidelines, completion axillary lymph node dissection (ALND) still is the standard of care after a positive sentinel lymph node in breast cancer. However, developments in pathologic staging and the proven benefit of adjuvant therapy undermines the need for ALND in all patients. The purpose of this retrospective study was to evaluate recurrence and survival in patients undergoing SLN biopsy alone versus SLN

with ALND. Methods: Patients with primary invasive breast cancer and a positive SLN were identified from 2 hospital breast cancer databases. Locoregional recurrences and disease free survival were examined. Results: We identified 670 patients with a positive sentinel node; 99 (14,8%) underwent SLN biopsy alone and 571 (85,1%) underwent SLN biopsy with ALND. The median follow up was 43 months. Patients were more likely to undergo SLN biopsy alone if they had a smaller metastasis size ($p < 0.05$). In patients with isolated tumor cells and micrometastases there was no significant difference in disease free survival between the patients that underwent SLN biopsy alone compared to those with SLN and ALND. However, survival in patients with macrometastases was significantly worse in the group undergoing SLN biopsy alone compared to those undergoing SLN and ALND ($p < 0.001$). Conclusion: Axillary lymph node dissection should not be omitted in patients with macrometastatic disease in the sentinel node. Omission of ALND in patients with micrometastases or isolated tumour cells in the sentinel node seems to be a safe option and should therefore be discussed with patients.



Overall survival curves for the SLN positive patients who did not undergo completion axillary lymph node dissection. Notice that the survival of the patients with a macrometastases is significantly worse than the other two groups.

P84

WITHDRAWN

P85

Analysis of Tumor Marker Response of Breast Cancer in the Setting of Neoadjuvant Chemotherapy S. Duggal,* K. Erb, T.B. Julian. *Allegheny General Hospital, Pittsburgh, PA.*

Background It is well documented that neoadjuvant chemotherapy (NC) for the treatment of locally advanced breast cancer allows for downstaging, downsizing, and introducing the potential for breast-conserving surgery. What is not well understood, however, is the effect of NC on estrogen receptor (ER), progesterone receptor (PR), and Her2/neu expression, and whether this is of clinical relevance in short- and long-term outcomes. Methods Upon IRB approval, a retrospective chart review was performed on patients with Stage II and III breast cancers treated with NC from January 2006 to December 2010. A total of 67 patients met eligibility criteria. ER, PR, and Her2/neu expression was analyzed in core biopsy specimens prior to NC, and in final specimens after definitive surgery. Her2/neu expression was validated by FISH analysis on all core biopsy and final surgical specimens with 2+ IHC staining. Results A total of 68 tumors were analyzed. Fifteen tumors achieved complete pathologic response. Of the remaining 53 tumors, tumor markers changed in 11 (18%) tumors. ER expression changed in 3 (5%), PR expression changed in 5 (9%), and Her2/neu expression changed in 3 (5%) tumors. ER, PR, and Her2/neu expression became positive 33%, 20%, and 66% of the time, respectively. Patient age, race, chemotherapy regimen, response to NC, and nuclear grade did not predict change. Conclusions For the individual tumor markers, there was a <10% change observed after NC, implying that NC contributes to this change, and no detrimental effect was observed. Rather, change in marker status may prove to be beneficial in terms of offering further endocrine or trastuzamab therapy to patients post surgical resection. This study poses the question of whether a switch in marker status after NC could be a prognostic indicator for disease free survival and overall survival. The course of tumor marker change requires further investigation. Additionally, future work regarding additional systemic therapy for residual disease burden based on these changes may improve outcomes.

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Predicting Success of Breast Conservation after Neoadjuvant Chemotherapy: What Factors Affect Surgical Outcome? E. Diego,* K.P. McGuire, A. Soran, M. Zuley, R. Bhargava, M. Bonaventura, R.R. Johnson, G.M. Ahrendt. *UPMC- Magee Womens Hospital, Pittsburgh, PA.*

Introduction Neoadjuvant chemotherapy (NAC) can be used to downstage primary breast cancers (BC) to facilitate breast conservation. After NAC, a significant number of patients will require a re-operation after initial lumpectomy despite post-NAC evaluation with MRI. This study seeks to identify factors that may predict this subset of patients to aid in surgical planning for breast conserving therapy (BCT). Methods Our Institutional Cancer Registry and radiology database were searched for patients with BC who received NAC with pre- and post-treatment MRI evaluation between 2004 and 2009. Re-excision rates were compared in relation to patient age, tumor histology, grade, size, receptor status, pathologic complete response (pCR: no residual invasive cancer on breast specimen and lymph nodes), and tumor size difference between post-NAC MRI and pathology using univariate and multivariate analysis. Results Two-hundred twenty seven patients received NAC for breast cancer and had MRI staging before and after NAC. All patients had intact tumors prior to chemotherapy initiation. Mean age was 49, (range 25-73). Mean post-treatment tumor size was 0.87, (range 0-4.5)cm. pCR was achieved in 51(25%) patients. The average discrepancy between tumor size by post-NAC MRI and pathology was 0.5 (range -3.5, 7.5)cm. BCT was attempted in 129 patients: 96 (74%) required no further surgery, 19(15%) patients required re-excision and 14(11%) needed completion mastectomy. On univariate analysis, tumor histology, receptor status, pCR and the tumor size difference between post-NAC

MRI and final pathology were significantly associated with the need for a second operation ($p<0.05$). Only the tumor size difference between post-NAC MRI and final pathology remained significant on multivariate analysis ($p<0.001$). Conclusion In the surgical planning for BCT in patients who received NAC, the tumor size difference between post-NAC MRI and final pathology significantly affect the success of BCT. This could be a result of the variable sensitivity of MRI in detecting residual disease for tumors of different receptor sub-types and is a subject for further investigation.

Univariate Analysis of Clinical/ Tumor Factors with Re-excision Rate

	No re-excision N (%)	Re-excision/ Completion Mastectomy N (%)	p value
Age(years), mean (min-max)	50 (25-73)	49 (35-65)	0.872
Tumor size difference between post-NAC MRI and final pathology (range)	0.4cm (-3.5, 3.6cm)	1.9cm (-2.0, 7.5cm)	<0.001
Histology			0.001
IDC	91(80)	22(20)	
ILC	3(30)	7(70)	
IMC	3(60)	2(40)	
unknown	0	1(100)	
Grade			0.579
I	3(60)	2(40)	
II	40(72)	16(28)	
III	52(80)	13(20)	
unknown	2(67)	1(33)	
pCR			0.001
+pCR	35(95)	2(5)	
-pCR	62(67)	30(33)	
Receptor Status			0.012
ER+	39(65)	21(35)	
ER-	58(84)	11(16)	

IDC: Invasive ductal carcinoma; ILC: invasive lobular carcinoma; IMC: invasive mammary carcinoma; pCR: pathologic complete response

P87

Long-term Follow-up of Axillary Recurrences after Negative Sentinel Lymph Node Biopsy: Effect on Prognosis and Survival B.J. Van Wely,[1]* J. Bulte,[1] S. Kasper,[1] G. Kuijt,[3] L. Strobbe,[2] H. De Wilt.[1]
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Introduction The treatment of the sentinel node (SN) positive axilla in breast cancer patients is under debate. An increasing number of patients do not undergo axillary treatment and as a consequence more patients will potentially develop axillary recurrences (AR). Untill now patients with an AR are relatively uncommon and outcome is not well known. This study was conducted to evaluate treatment and prognosis of these patients. Patients and methods A retrospective analysis of the Dutch cancer registry of 16 high volume breast cancer units was used to identify patients with an AR after negative SLNB operated on between 2002-2004. Results After a median follow up of 84 months (range 17-154) we identified 54 patients with an AR. In 45/54 patients the primary tumor was an invasive ductal carcinoma. The median primary tumor size was 19mm (range 1-55). Estrogen receptor was positive in 72%, BR grade 2-3 was present in 44/54 patients. Nineteen patients (35%) were treated with breast conserving therapy. Six patients received adjuvant chemotherapy (CT), 10 patients adjuvant hormonal therapy (HT) and 4 patients received both. Median time between SLNB and detection of the AR was 30 months (range 3-79). Axillary disease was treated with Axillary Lymphnode Dissection (ALND) in 45 patients and revealed a median of 3 positive nodes (range 1-24). In nine patients the axilla was not operated on. Three patients received external beam radiation therapy (EBRT) and 6 patients only received systemic therapy. At time of detection of the AR, a total of 7 patients had proven distant metastases. After a median follow up "post-recurrence" of 47 months (range 3-118), 19 additional patients developed distant disseminated disease and 22/54 patients (41%) died. Conclusion Almost 50% of patients diagnosed with an AR after negative SLNB present with distant metastases or develop distant metastases shortly during follow-up. The prognosis of these patients is therefore poor, indicating the importance of close follow up when axillary treatment is not performed in SLNB positive patients.

P88

Immediate and Delayed Complications of Nipple Sparing Mastectomy (NSM) J.D. Lewis,* P.D. Smith, J.V. Kiluk, W. Sun, C. Laronga. *H Lee Moffitt Cancer Center & Research Institute, Tampa, FL.*

Background: Studies demonstrate technical feasibility and short-term oncologic safety of NSM. However, a dearth of data exists regarding immediate/delayed complications of NSM with immediate reconstruction. Our objective is to review our institutional experience with complications of NSM. Methods: An IRB approved retrospective review of prospectively gathered women having NSM with/without immediate reconstruction was conducted. Indications for NSM were either prophylaxis (risk reduction) or breast cancer treatment. Data reviewed included clinico-pathologic features, operative procedures, immediate post-operative and delayed complications, and outcomes. Results: From 2005-2010, 111pts had NSM with a median age of 48.5 years (range: 18-82); median BMI of 23 (range: 17-34). The majority had bilateral NSM (76pt/111pt, 68%) totaling 111pts having 187 NSM (our study cohort). 92/187(49.1%) NSM were performed for cancer with a median invasive tumor size of 13.3mm (range: 0.5-100mm). Four patients had 5 NSM without any reconstruction. Reconstruction was tissue expanders (TE) alone (75/187 NSM, 40.1%), TE with dermal matrix (85/187, 45.5%), TE with latissimus flap (9/187, 4.8%) or autologous flap alone (13/187, 6.9%). 70/111pts experienced a complication(s) totaling 162 events (Table). Some pts had a combination of complications. Intraoperative nipple removal for atypia of cancer was performed in 3pts (4 nipples). Unique immediate complications (<30days) included epidermolysis (defined as scabbing /scaling of nipple tip), partial nipple loss, and complete nipple loss. Unique delayed complications included malposition/asymmetry of nipple and depigmentation of nipple. Delayed infections were seen at a median time of 7 months (range: 1-51) and unrelated to second stage procedures. Other complications (Table) are related to reconstruction itself. Mean follow-up was 21 months for 111 pts with 174/187 (93%) NSM ultimately maintaining their nipples. Conclusions: NSM may be an option for women with breast cancer or as prophylaxis. As oncologic safety data accrues, attention must also be given to minimizing immediate/delayed complications, especially if ultimately they result in sacrifice of the nipple.

Complications (total=162 events)	Immediate (<30 days) (n, %)	Delayed (>30 days) (n, %)
Epidermolysis	49 (30.2%)	4 (2.5%)
Partial nipple loss	10 (6.2%)	5 (3.1%)
Complete nipple loss	1 (0.6%)	1 (0.6%)
Skin necrosis / loss	11 (6.8%)	5 (3.1%)
Infection requiring TE removal	2 (1.2%)	21 (13%)
TE leak or malposition	6 (3.7%)	10 (6.2%)
Hematoma / seroma	9 (5.6%)	3 (1.9%)
Depigmentation	0	2 (1.2%)
Asymmetry of nipple	7 (4.3%)	13 (8%)
Infection requiring antibiotics (PO / IV)	3 (1.9%)	9 (5.6%)
Capsular contracture / deformity	0	11 (6.8%)

P89

Intraoperative Digital Specimen Mammography Decreases Operative Time M.G. Valero,[1] M.S. Camp,[1]* N. Opara,[2] K. Benabou,[2] L. Cutone,[2] L. Dominici,[1] M. Golshan.[1] *1. Breast Surgery, MGH/Brigham, Boston, MA; 2. Dana Farber Cancer Institute, Boston, MA.*

Introduction: Traditionally, physicians have used standard specimen mammography (SSM) to confirm complete excision of a wire localized breast biopsy. Recently, many surgeons have started using intraoperative digital specimen mammography (IDSM) to provide immediate specimen evaluation in the operating room (OR). The goal of our study was to compare the length of operative time with the use of SSM versus IDSM. Methods: A retrospective chart and electronic operating room record review was performed of 344 patients from a single breast surgeon at a quaternary care academic center from 2003

to 2010. Patients underwent wire localized excisional biopsy or wire localized lumpectomy without lymph node evaluation. The specimens were imaged using either SSM or IDSM. Operative time, defined as time of incision until time of closure, was compared between surgical procedures using SSM versus IDSM. Images were reviewed by both the surgical oncologist and the breast imager to confirm appropriate excision. Results: Of the 344 patients, 230 underwent SSM and 114 patients underwent IDSM following excision of a wire localized breast biopsy specimen. Demographics and distribution of preoperative diagnoses were similar between the two groups. 22% of patients in the SSM group and 17% of patients in the IDSM group had a preoperative diagnosis of invasive cancer or DCIS; 78% of patients in the SSM group and 83% of patients in the ISDM group had a preoperative diagnosis of indeterminate or benign (p=0.21). Median operative time in the SSM group was 50 minutes compared to 37 minutes in the IDSM group (p<0.001). Conclusion: Operative times for wire localized excisional biopsy or lumpectomy are significantly shorter with the use of IDSM versus SSM. Decreased operative time with the use of ISDM can lead to beneficial downstream effects including decrease in anesthetic time, decrease in operating room charges, and an increase in surgeon productivity.

Patient Characteristics and Operative Time

	SSM	IDSM	p value
Number	230	114	
Age (median)	51 (Range 22-88)	52 (Range 26-85)	0.18
Preoperative diagnosis			0.21
Cancer (invasive/DCIS)	50 (22%)	19 (17%)	
Indeterminate/benign	180 (78%)	95 (83%)	
Operative time (median, in minutes)	50	37	<0.001

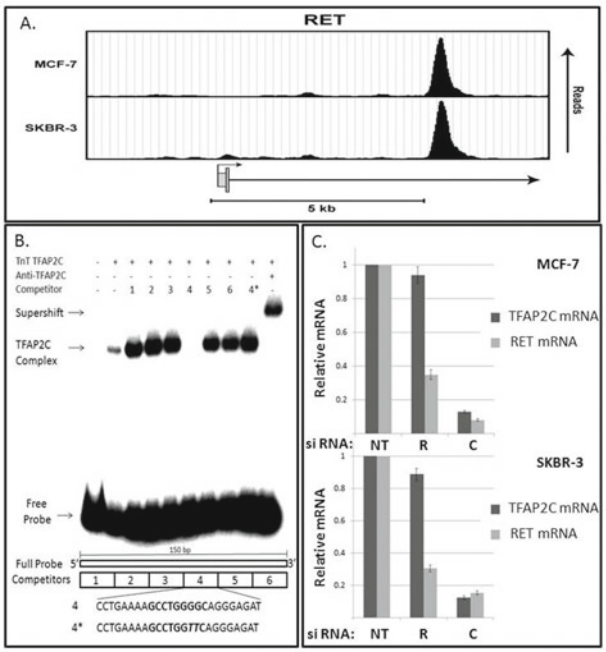

Figure 1 TFAP2C Binding of the RET Regulatory Region and TFAP2C dependent RET expression. A. ChIP-seq data for TFAP2C genome browser graphical output for the RET gene for MCF-7 and SKBR-3. **B.** Map of the promotor region targeted by TFAP2C with oligo competitors and gel shift with 150 bp probe using cloned TFAP2C protein. Bands are for free probe, TFAP2C/probe complex and complex antibody supershift. **C.** TFAP2C and RET expression in MCF-7 and SKBR-3 after transfection with siRNA: non-targeting (NT), RET (R), or TFAP2C (C).

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Expression of the RET Proto-oncogene is Regulated by TFAP2C in Breast Cancer Independent of Estrogen Receptor P.M. Spanheimer,* G.W. Woodfield, M.V. Kulak, T.B. Bair, R.J. Weigel. *Surgery, University of Iowa, Iowa City, IA.*

Introduction: Inherited mutation of the RET receptor tyrosine kinase causes the MEN2 syndromes and Hirschsprung's disease. In breast cancer, RET is expressed as part of the estrogen receptor (ER) cluster and recent reports have shown a role for ER in regulation of RET expression. TFAP2C is a transcription factor that regulates the expression of key breast cancer genes including ER, ER cluster genes, and HER2. It is not clear if RET is a direct target of TFAP2C or a secondary target through regulation of ER. We proposed to examine the role of TFAP2C in the regulation of RET. Methods: Binding sites for TFAP2C in primary breast cancer cell lines were identified by chromatin immunoprecipitation sequencing (ChIP-seq). DNA binding was characterized by gel-shift assay with cloned TFAP2C protein. Small interfering RNA (siRNA) knockout of RET and TFAP2C was performed in ER+ MCF7 and ER- SKBR3 cell lines. TFAP2C and RET mRNA were measured using real-time polymerase chain reaction. Results: ChIP-seq identified a binding peak for TFAP2C 5.2 kb downstream from the transcriptional start site within the first intron of the RET gene (Figure 1A). Using gel shift a 150 bp probe generated from the ChIP-seq peak was found to bind TFAP2C. Competitors spanning the probe localized binding of TFAP2C to a 25 bp region containing an AP2 family consensus binding site. Mutation of the site (competitor 4*) failed to compete confirming the location of TFAP2C binding in the RET gene (Figure 1B). Knockdown of TFAP2C by siRNA in ER+ MCF7 cells resulted in significant down regulation of RET mRNA compared to non-targeting (NT) siRNA (0.09 vs 1.0, p<0.001). Interestingly, knockdown of TFAP2C in ER- SKBR3 cells also led to a significant reduction in RET mRNA compared to NT siRNA (0.14 vs 1.0, p<0.001), Figure 1C. Conclusions: TFAP2C regulates expression of the RET proto-oncogene through a binding site in the first intron. Investigation in ER+ and ER- breast carcinoma cell lines demonstrates that regulation occurs independent of ER. These data provide further evidence that TFAP2C targets a set of genes in breast cancer critical to cell proliferation and tumor behavior.

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Completion Axillary Node Dissection in Elderly Women with Early Stage Breast Cancer S. Javid,* D.R. Flum, H. He, K.E. Calhoun, B.O. Anderson. *Surgery, University of Washington, Seattle, WA.*

Introduction: The role of completion axillary lymph node dissection (cALND) for elderly women with sentinel lymph node-positive (SLN+) invasive breast cancer is questioned, because cALND causes morbidity and is unlikely to improve survival. This study examines the use of sentinel lymph node biopsy (SLNB) and cALND and their impact on therapeutic decision-making and outcome among elderly women in the U.S. Methods: Using the SEER-Medicare database, we reviewed records of women age >65 diagnosed with stage I or II breast cancer from 1998-2005. Adjusted Cox proportional hazards and multivariate logistic regression were used to assess the effect of cALND on survival and to identify predictors of cALND in SLN+ patients. Results: 24,023 elderly patients underwent SLNB, with its utilization increasing from 23.1% to 78.0% during the 7-year study period. Earlier year of diagnosis, greater node involvement (macro vs. micrometastasis), younger age, registry location, and larger tumor size were all associated with a significantly higher odds ratio of undergoing cALND. Omission of cALND among SLN+ patients increased from 0.4% in 1998 to 12.4% in 2005. At median follow-up of 44 months, cALND in SLN+ patients did not impact overall or breast cancer-specific survival (HR 1.22, 95% CI 0.76-1.96). SLN+ patients who underwent cALND were more likely to receive adjuvant chemotherapy than were patients who had SLNB alone (OR 1.8, 95% CI 1.45-2.24). However, younger age, ER negative status, and lower Charlson Comorbidity Index score were all more strongly associated with receipt of chemotherapy than was the extent of axillary surgery (OR 18, 4.2, and 2.6, respectively). Chemotherapy was not observed to influence breast cancer-specific survival (p>0.6) in this elderly population. Conclusions: Omission of cALND does not appear to impact 5-year survival among older SLN+ breast cancer patients. Age, comorbidities and ER status were stronger determinants of chemotherapy usage than was extent of axillary surgery. Consideration should be given to omitting cALND

in older patients with early stage breast cancer, particularly if the findings of cALND will not influence adjuvant therapy recommendations.

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Association of State and Trait Anxiety and Choice of Surgery in Women with Hereditary Breast Risk who Develop Breast Cancer J.C. Boughey,* T.L. Hoskin, L.C. Hartmann, T.M. Allers, A.C. Degnim, C.I. Williams, M. Frost. *Surgery, Mayo Clinic, Rochester, MN.*

Background: Women with hereditary breast cancer risk who develop breast cancer face complex surgical decisions related to their index breast and their contralateral breast. The aim of this study was to prospectively evaluate the state and trait anxiety scores of women and to examine associations between anxiety scores and treatment choice. Trait anxiety, a stable personality characteristic, is the tendency to perceive a situation as threatening while state anxiety is a temporary response to a specific situation. Methods: Women with hereditary breast cancer risk diagnosed with unilateral breast cancer were enrolled in a prospective decision making questionnaire study. Questionnaires were completed prior to initial breast clinic visit and 6 months after surgery. Anxiety was measured using the Spielberger State-Trait Anxiety Inventory. Trait anxiety was assessed preop; state anxiety was assessed both preop and postop. Results: 56 women completed both questionnaires. Mean age was 51 (range 27-84). Stage distribution was 4 (7%) stage 0, 27 (48%) stage I, 16 (29%) stage II, and 9 (16%) stage III. Surgical treatment was lumpectomy in 27 (48%), unilateral mastectomy in 14 (25%), and bilateral mastectomy in 15 (27%). Mean preoperative state anxiety was significantly higher for the bilateral mastectomy group compared to both the lumpectomy ($p = 0.02$) and unilateral mastectomy ($p = 0.01$) groups. The difference between the mastectomy groups remained significant after adjusting for age and stage ($p = 0.04$). Six months postop, there was no longer a significant difference in state anxiety among the surgery groups ($p = 0.55$). The bilateral mastectomy group had a significant drop in state anxiety between preop and postop ($p = 0.0006$). Mean preop trait anxiety was 33.4 (range 21-53), and did not differ significantly among the surgery groups (Table 1). Conclusion: Among unilateral cancer patients with a family history, those who chose bilateral mastectomy had higher preop state anxiety but observed a significant drop in state anxiety by six months postop. Six months postop state anxiety scores were similar among surgical groups.

Variable	Lumpectomy	Unilateral Mastectomy	Bilateral Mastectomy
Age, mean (SD)	54.9 (12.2)	51.1 (15.2)	44.2 (10.3)
Stage, n (%)	2 (7.4)	1 (7.1)	1 (6.7)
	18 (66.7)	4 (28.6)	5 (33.3)
	7 (25.9)	7 (50.0)	2 (13.3)
	0	2 (14.3)	7 (46.7)
Preop state anxiety score, mean (SD)	46.0 (10.5)	44.0 (12.6)	54.7 (10.8)
Postop state anxiety score, mean (SD)	32.9 (9.8)	34.9 (10.0)	36.4 (10.9)
Trait anxiety score, mean (SD)	34.3 (6.8)	30.9 (6.6)	33.9 (5.9)

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Exploration of Lymphatic Biomarkers in the Axillary Tissue of Women with Breast Cancer S.A. McLaughlin,* A. Parker, M. Arnold, M. Murray, S. Bagaria, T. Gibson, N. Diehl, J. Crook, J. Nguyen, P. Anastasiadis. *Department of Surgery, Mayo Clinic, Jacksonville, FL.*

Background: Recent discovery of lymphatic biomarkers has the potential to improve understanding of the lymphatic environment and help explain nodal metastases. We sought to characterize a panel of lymphatic biomarkers in the axillary tissue of women with breast cancer. Methods: From 12/08 to 12/09 we collected fresh frozen extra-nodal axillary lymphatic tissue from 73 women with Stage 0-3 breast cancer. Using immunohistochemistry, we stained for LYVE1 (lymphatic endothelial marker), VEGF-C (lymphangiogenesis activator), VEGFR3 (lymphangiogenesis receptor), and MMP9 (extracellular matrix effector) and quantified expression as a percent burden for each biomarker using digital microscopy. We used Wilcoxen rank sum tests to evaluate the association of biomarker expression in axillary tissue with clinicopathological variables and with expression of each biomarker in matched samples of breast tumor and axillary lymph node from each patient. Results: Of 73 women, 36 (49%) were node positive (LN+) and 37 (51%) node negative (LN-). In axillary tissue, the expression of LYVE1 increased with age (<50yo 9%, 50-70yo 12%, >70yo 16%, p=0.02). However, no other association between axilary tissue expression of any biomarker and tumor type, BMI, or tumor size existed (all p>0.12). When compared to LN- women, LN+ women had significantly higher expression of VEGFR3 and MMP9 and a trend towards lower LYVE1. In contrast to axillary tissue expression, the breast tumors demonstrated the exact opposite trends of biomarker expression as LN+ women had lower VEGFR3 and MMP9 (although all p>0.16) and significantly higher LYVE1 (p=0.03) compared to LN- women. No significant trends existed in the expression of any of the biomarkers in the lymph nodes. Conclusions: We observed opposing trends of lymphatic biomarker expression in breast tumor and axillary tissue. If confirmed, changes in the extra-nodal axillary tissue supported by over-expression of MMP9 and VEGFR3 may create an environment promoting metastatic tumor spread to axillary nodes. Further investigation into whether this difference is an inherent patient quality or one that is induced by the primary tumor is warranted.

	LN-	LN+	
Variable	Median (IQR)	Median (IQR)	p
Breast Tumor			
VEGFR3	8.12 (3.1, 35.2)	2.93 (0.7, 16.3)	0.16
VEGFC	0.27 (0.08, 0.64)	0.13 (0.05, 0.37)	0.33
MMP9	43.12 (25.9, 53.8)	29.48 (24.5, 44.9)	0.25
LYVE1	0.30 (0.21, 0.43)	0.41 (0.29, 0.87)	0.031
Axillary Tissue			
VEGFR3	11.5 (9.4, 16.7)	19.7 (9.8,27.1)	0.003
VEGFC	6.01 (4.2, 7.5)	6.22 (4.1,7.6)	0.86
MMP9	0.60 (0.31, 1.02)	1.30 (0.53, 2.79)	0.001
LYVE1	13.57 (9.1, 17.5)	11.53 (7.1, 16.2)	0.21

P-values obtained from Wilcoxon rank sum test

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Nipple Sparing Mastectomy for the Treatment of Breast Cancer: A Systematic Review B.S. Mota,[1]* R. Rieira,[2] A.N. Atallah,[2] J.B. Bevilacqua.[1] *1. Hospital Sirio Libanês, São Paulo, SP, Brazil; 2. Universidade Federal de São Paulo - UNIFESP, São Paulo, SP, Brazil.*

Background: The efficacy and effectiveness of Nipple Sparing Mastectomy (NSM) for the treatment of breast cancer (BC) are still questionable. We undertook this systematic literature review to search the best scientific evidence of NSM for the treatment of BC. Methods: Electronic search was conducted using the Mesh terms for "nipple sparing mastectomy" in the following databases: Cochrane Breast Cancer Group Specialized and Controlled Trial Registers, MEDLINE, EMBASE, LILACS and The WHO International Clinical Trials Registry Platform. Inclusion criteria were randomized or quasi-randomized studies of in situ or invasive BC. The studies were selected and data collected by two independent authors and when there was a discrepancy, a third author conducted the analysis. Primary endpoint was overall survival (OS). Secondary endpoints were local recurrence (LR) rate, surgical complications, cosmetic results and quality of life (QoL). The data extraction was performed using the RevMan 5.0 software according to Cochrane Handbook for systematic reviews 5.0.0 and then, descriptive analysis of the data was performed. Results: 591 abstracts were identified (June 29th 2011). No randomized or quasi randomized studies were identified. Subsequently, the next levels of evidence considered were cohort and retrospective case series. 27 publications fulfilled these criteria. There were 4 comparative cohorts, 9 non comparative cohorts and 14 case series. We used two epidemiological questionnaires to access quality in cohort studies ("Black Instrument" and "New Castle Ottawa Scale"). Efficacy was evaluated by comparative cohorts, and other outcomes, by cohort and case series studies. The total number of patients submitted to NSM in these studies was 3 820. The mean quality score was 0.77 (Min–Max: 0.52–0.89). (see table) Conclusion: The published data on NSM is still preliminary, based on low level of evidence and low quality score studies. Therefore, NSM for the treatment of BC outside study protocols is unwarranted. Prospective randomized trials and/or prospective well designed cohort studies addressing the efficacy and effectiveness of this procedure are necessary.

Outcome	# of Studies	FU (Months)		OS %		LR %		SC %		QoL %	
		Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
OS	6	30	180	76	100						
LR	24	8	180			0	28				
SC	18	8	60					5	22		
QoL	7	16	60							64	80

#, Number; FU, Follow up; OS, Overall Survival; LR, Local Recurrence; SC, Surgical complications; QoL, Quality of life; Min, Minimum value; Max, Maximum value

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Predictors of Variability between Primary Breast Cancers and Their Ipsilateral Breast Tumor Recurrences (IBTR) N.S. Kapoor,[1]* J. Yoon,[1] J. Shamonki,[2] M. Sim,[1] A. Chung,[3] A.E. Giuliano.[3] *1. John Wayne Cancer Institute, Santa Monica, CA; 2. St. John's Medical Center, Santa Monica, CA; 3. Cedars Sinai Medical Center, Los Angeles, CA.*

Background: IBTR that occur greater than five years from presentation of initial primary tumor (PT) or distant from the PT site are generally thought to represent new primaries rather than true recurrences. To better understand the biology of these different IBTRs, we compare features of the PT to IBTR and report the influence of time and location. Methods:IBTR surgically managed at our institute between 1980-2008 with pathology review were studied. Histologic type, grade, and ER/PR/Her2 status of both PT and IBTR are compared and multivariabe analysis (MVA) using PT characteristics, lymph node status, adjuvant treatment, location of IBTR, and time to recurrence is reported. Results:Seventy-five patients with 150 tumors were included. Median patient age was 52(range 26-86) and median PT size was 1.7cm(range 0.1-7cm). Median time to recurrence was 37 months(range 5-198), 24 IBTRs occurred after 5 years of PT presentation. IBTR location was known for 64 and was the same as the PT for 44(68.8%). ER/PR status was available for 47 pairs and HER2 in 41. Compared to the PT, 90% of IBTR were the same histologic type but those developing after 5 years were significantly more likely to be different histologic type than earlier, 25% vs 2%($p<0.004$). IBTRs in the same location as the PT were more often the same histologic type as the PT compared to different locations, 86% vs 65%($p<0.009$). In addition, larger PTs were more likely to have similar IBTR than smaller($p<0.03$). On MVA, greater disease free interval(DFI) and small size predicted different IBTR histology($p<0.02$ each). Same histology and receptor profile was seen in 70%. Adjuvant therapy was given to 77% of patients and this did not predict tumor similarities. Conclusions:Differences are more common between the PT and IBTR with longer DFI, however 75% will still be the same histologic type and 70% will have the same receptor profile even after 5 years. Moreover, 24% of IBTRs similar to the PT were not same site. This suggests that even late or different site IBTR may be a PT recurrence. Alternatively, it may be that the breast tends to form the same tumor type irrespective of time, location, or treatment.

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Automated Technique for Imprint Cytology Interpretation of Surgical Margins for Breast Cancer M. Ruidiaz, A. Kummel, J. Wang-Rodriguez, S. Blair.* *University of California San Diego, La Jolla, CA.*

Background: Breast conservation therapy (BCT) is the standard treatment for breast cancer; however, 20-50% of operations have a positive margin leading to secondary procedures. The standard of care to evaluate surgical margins is based on permanent section. Imprint cytology (touch prep) has been used to evaluate surgical samples, but require an experienced cytopathologist for interpretation. An automated image-based process has been developed to identify cancer cells on touch preps. Methods: We prospectively performed imprint cytology on surgical margins during lumpectomy operations for breast cancer in addition to permanent section on 127 patients. We found 18 positive/close margin cases and an 8 slide training subset was culled. The results of the H&E imprint cytology automated analysis were compared to permanent section interpretation. Linear discriminate analysis (LDA) was used to identify cell populations (Fig 1). Results: The training set was based on an 8 slide positive/close margin subset, which was manually identified for cells belonging to the class of either cancer cells, normal cells, or junk/debris objects. Final class proportions were 12%, 28% and 60% for the classes respectively. Because these slides were derived from a true cauterized margin, a disproportionate selection of junk/debris objects over other class types occurs. LDA performance analysis yielding an overall 91% accuracy. Individual class performance was 84%, 87% and 94% for cancer, cell and debris objects, respectively. These most important descriptors, in terms of accuracy improvement, are inner (nuclear) color (23%), outer (cytoplasm) color (15%), shape (12%), grey intensity (9%) and localized area (5%). The automated imprint cytology identified 50% of positive margins which is comparable to the manual analysis of these this slide set. Conclusions: This preliminary study using an automated system for intra-operative interpretation does not require a cytopathologist and shows that rapid imaging can correctly identify positive margins from surgical specimens. Therefore, automated determination of cellularity in touch prep is a promising technique for future margin interpretation of BCT.

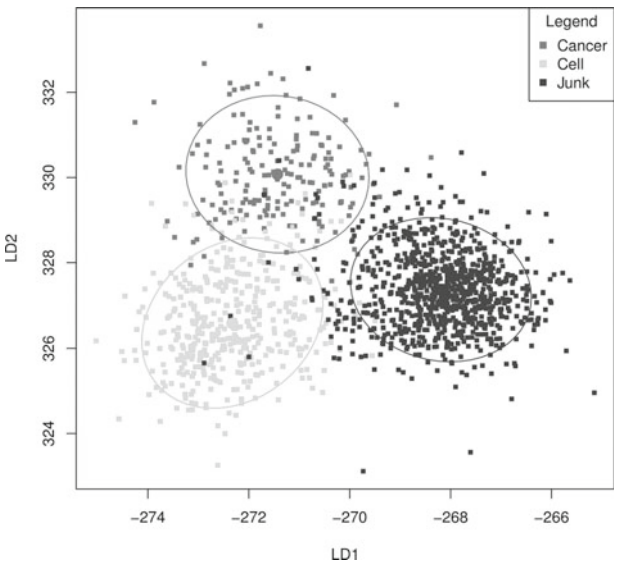

Figure 1: Class separation in LDA-transformed space showing Cancer (red), Normal Cell (Green), and Junk/Debris (Blue) clustered separately. 80% normal probability ellipses for each class is overlaid.

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The Impact of Federal and State Policy Changes on the Likelihood of Immediate Breast Reconstruction following Mastectomy R.L. Yang,* R.R. Kelz, C.E. Reinke, G.C. Karakousis, B.J. Czerniecki, A.S. Newman, I.C. Lin, L.C. Wu. *University of Pennsylvania School of Medicine, Philadelphia, PA.*

Background: In response to research demonstrating improved quality-of-life among breast cancer survivors who have had reconstruction, several federal and Pennsylvania state policies were passed in the years of 1997 to 2000 mandating insurance coverage of all post-mastectomy breast reconstruction (PMBR). The impact of these policies on the likelihood of PMBR has not yet been evaluated. Methods: Patients greater than 18 years old who had a mastectomy were identified in the Pennsylvania Health Care Cost Containment Council inpatient database from 1994 to 2004. International Classification of Disease-9 procedure codes were used to identify patients who underwent PMBR. Reconstruction rates were compared before (1994-1997) and after (2001-2004) the policy changes using a chi-square test. Univariate and multivariate analyses estimated the relative odds of PMBR with adjustment for potential confounders (age, race, median income, Elixhauser comorbidity index, and hospital reconstruction volume). The expected numbers of PMBR for the study time interval were determined by standardizing to the 2004 reconstruction rate. Results: During the study time interval 35,206 patients had a mastectomy with 8,411 (23.89%) undergoing PMBR. Age, race, median income, comorbidity index, and hospital reconstruction volume were all significantly associated with reconstruction rate ($p<0.05$). The proportion of patients undergoing PMBR increased from 2,062 (18.49%) prior to policy changes to 4,308 (27.58%) following policy changes ($p<0.001$). The adjusted model showed that patients were more likely to undergo PMBR following the policy changes (OR 2.13, 95% CI 1.98-2.29). Using the 2004 PMBR rate for standardization, the expected number of total reconstructions from 1994 to 2004 was 10,215, indicating that 1,802 more patients would have undergone reconstruction. Conclusions: The likelihood of PMBR has increased significantly since the policy changes around the turn of the century but the absolute rates remain low. Further studies are needed to evaluate the relative contribution of cultural issues, accessibility and educational disparities to the underuse of PMBR.

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Booster Inoculations Safely Sustain the Immune Effects of a CD4-targeted Peptide Cancer Vaccine T.J. Vreeland,[1]* D.F. Hale,[1] G.T. Clifton,[1] A. Sears,[1] S.A. Perez,[2] A. Ardavanis,[2] N. Pistamaltzian,[2] G. Rellias,[2] S. Ponniah,[3] M. Papamichail,[2] G.E. Peoples,[1] E.A. Mittendorf.[4] *1. Surgery, San Antonio Military Medical Center, Ft. Sam Houston, TX; 2. Saint Savas Cancer Hospital, Athens, Greece; 3. Cancer Vaccine Development Program, Uniformed Services University of the Health Sciences, USMCI, Bethesda, MD; 4. U.T. MD Anderson Cancer Center, Houston, TX.*

Introduction: Vaccines are being developed to treat cancer or prevent recurrences. Concerns exist over the durability of immunity. We are vaccinating pts with a CD4-targeting peptide, AE37, the Ii-Key hybrid of the HER2 peptide AE36 (HER2: 776-790). We present the impact and safety of boosters in a prospective, randomized, single-blind, phase II trial of AE37 for the prevention of breast cancer (BrCa) recurrence. Methods: After standard therapy, disease-free, high-risk BrCa pts got AE37+GM-CSF (Vaccine (V)) or GM-CSF alone (Control (C)) in 6 monthly doses. Some got voluntary boosts (Boosted (B)) (V receiving AE37+GM-CSF and C receiving GM-CSF) every 6 mos after the primary vaccine series (PVS). Immunity was monitored in vitro with AE37 peptide-specific T cell proliferation by [3H]-thymidine incorporation assay and in vivo by the size of local reaction (LR) to the dose. This was done before (R0), mid-series (R3), at the end of (R6), and at 6 (RC6) and 12 (RC12) mos after PVS. Results: 240 pts are enrolled (US=139, Greek=102; V=101, C=139), and 87 boosted (V=48, C=39). 97% of local and syst. toxicities have been grade 1 or 2. In the C, there was 2% grade 3, and 0.4% grade 4 max toxicity, while the V had 3% grade 3 (none in B) and no grade 4. There were no sig. differences between groups. V pts increased mean+SE proliferation response to AE37 from R0 to R6 of 2054±466 to 7051±1245 cpm ($p<0.01$), compared to a drop of 2913±57 to 2400±48 cpm($p=0.75$) in the C pts. The increase waned in the non-B pts after PVS(2273±649 to 4574±1144 cpm, R0 to RC12 $p=0.17$); it was maintained in B(1589±388 to 7734±1526 cpm, R0 to RC12, $p<0.01$). There were similar in vitro results in US and Greek pts. V pts increased their LR at R6(31.6±2.7 mm R0 to 47.6±4 mm R6, $p<0.01$), while C pts did not significantly(17.3±2.5 mm R0 to 29.1±7 mm R6, $p=.12$). B V pts had increased LRs R0 to RC12(31.6±2.7mm vs 45.7±6 mm, $p<.01$), while non-B V pts did not(17.3±2.5 mm vs 13.8+5 mm, R0 to RC12 $p=0.09$). Conclusion: The AE37 peptide vaccine and boosters are safe with toxicities that are attributable to GM-CSF. The AE37 vaccine elicits strong HER2-specific immune responses that can be maintained with boosters.

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Patterns of Use of Neoadjuvant Chemotherapy: Clinical and Pathologic Characteristics of Patients Enrolled in ACOSOG Z1071 J.C. Boughey,[1]* V.J. Suman,[2] E.A. Mittendorf,[3] L.G. Wilke,[4] A.M. Leitch,[5] T.A. Buchholz,[3] B.G. Haffty,[6] W.F. Symmans,[3] D.R. Byrd,[7] K.K. Hunt.[3] *1. Surgery, Mayo Clinic, Rochester, MN; 2. Mayo Clinic, Rochester, MN; 3. MD Anderson Cancer Center, Houston, TX; 4. University of Wisconsin, Madison, WI; 5. University of Texas SouthWestern, Dallas, TX; 6. The Cancer Institute of New Jersey, New Brunswick, NJ; 7. University of Washington, seattle, WA.*

Background: Neoadjuvant chemotherapy (NAC) improves surgical options in operable breast cancer and provides an assessment of response. The accuracy and feasibility of sentinel node (SN) surgery after NAC for node-positive patients at presentation remains a question. The American College of Surgeons Oncology Group (ACOSOG) conducted Z1071 to evaluate SN surgery in this setting. We report here the patient and tumor characteristics of patients enrolled in Z1071. Methods: Z1071 was a prospective phase II multicenter cooperative group trial which accrued 756 patients from July 2009 to July 2011. Pre-treatment patient and tumor characteristics are summarized. Results: Complete data is available on 738 patients. Ages ranged from 23 to 93 years, with 50% less than age 50. Racial distribution was White: 80.8%; African American: 13.8%; Asian: 2.6%; American Indian/Alaska Native: 0.4%. Comorbid conditions included cardiac disease (26.3%), diabetes (8.3%), and arthritis (6.5%). Clinical tumor stage at presentation was T0: 1.2%, T1: 13.5%; T2: 54.3%, T3: 25.3%, T4non-inflammatory: 5.1%. All patients were biopsy proven node positive at presentation, clinical stage was N1 in 90.1%; N2 in 8.6%. Diagnostic lymph node biopsy at diagnosis was FNA in 37.1% and core needle biopsy in 62.9%. Tumor subtypes were: triple negative (TN): 24.1%, HER2+: 29.1%; hormone responsive (HR+), HER2neg; 45.2%. Among the 483 women with cT1 or cT2 disease, 53/97 (54.6%) of T1 tumors and 210/386 (54.4%) of T2 tumors had either TN or HER2+ disease. Grade 3 tumors were seen in 77% of TN, 60% of HER2+ and 40% of HR+/HER2neg. Clinical T stage and N stage were similar across the tumor subtypes. Conclusion: Patients enrolled on ACOSOG Z1071 encompassed a wide range of ages and clinical T stages. Physicians preferentially enrolled TN and HER2+ patients resulting in higher representation from these groups than standard distribution of breast cancer subtypes both in the pre and postmenopausal patients. With NAC use across the whole biologic spectrum defining the role of axillary surgery in these patients will be critical in local-regional management.

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Oncoplastic Breast Surgery: Oncologic Benefits and Limitations D. Wedman,* T. Zhang, A. Arnaout. *General Surgery, Ottawa Hospital, Ottawa, ON, Canada.*

BACKGROUND Breast conservation therapy with lumpectomy is a valuable part of breast cancer treatment, with equivalent survival outcome to that of mastectomy. Recently, oncoplastic surgery has been popularized as a method to improve margins and yield better aesthetic outcomes when traditional lumpectomy either anticipates poor results or is not possible. This study was undertaken to examine the oncologic benefits and limitations of this technique in providing adequate breast conservative therapy. METHODS This was a retrospective review of the surgical outcomes of all patients offered breast conserving therapy at a tertiary care hospital from 2008 to 2011. Patients were divided into three groups: the Traditional lumpectomy group (no attempt was made to close the defect), Oncoplastic level I group (less than 20% of the breast tissue excised; general under-mining to close defects) and Oncoplastic level II group (skin resection, greater than 20% of the breast tissue excised) which included batwing resection, Binelli mastopexy, reduction and J/raquet mammoplasties. RESULTS A total of 237 patients had lumpectomies during this period; 106 patients in the Traditional, 97 patients in level I, 34 patients in the level II Oncoplastic group. There was no significant difference in the age, cancer stage, proportion of DCIS versus invasive disease, histology of invasive disease, ER, PR, Her 2 status and postoperative complication rate between all three groups. No statistically significant difference in the ability to get wide margins ($p=0.09$) or in the re-excision rate ($p=0.66$) between either of the oncoplastic and the traditional groups. However, the level II Oncoplastic group had a better ability to provide adequate resection for multifocal ($p=0.03$) and larger T stage ($p=0.01$) tumors, but only when DCIS was excluded. Finally, oncoplastic surgery achieved adequate resection of tumors in the lower inner/lower outer quadrants ($p=0.01$). CONCLUSION Oncoplastic surgery level II techniques extend the scope for breast-conserving surgery, allowing for resection of the larger and multifocal tumors in traditionally cosmetically difficult quadrants of the breast, without greater postoperative complication rates.

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Phenotype of Pure DCIS in BRCA Mutation Carriers R.E. Roses,* H.M. Kuerer, C.T. Albarracin, S.A. Lari, B.K. Arun. *UT MD Anderson Cancer Center, Houston, TX.*

Background: The frequencies of specific invasive breast cancer subtypes are different in BRCA mutation carriers compared to non-carriers. Most notably, BRCA1 mutation carriers have a predilection for developing triple negative tumors. The phenotypes of pure ductal carcinoma in situ (DCIS) lesions in BRCA mutation carriers, however, have not been well characterized. The purpose of this study was to determine the hormone and growth factor expression profiles of pure DCIS lesions in patients with BRCA mutations. Methods: Seventy-five patients referred for genetic counseling between 2003 and 2011 with pure DCIS were included in this study. All of these patients underwent genetic testing for BRCA1 and BRCA2 mutations. In many cases, estrogen receptor (ER), progesterone receptor (PR) and HER-2/neu expression in the lesions were assessed by immunohistochemistry. Using the available immunohistochemical data, DCIS lesions were characterized as luminal (expressing ER or PR), HER2 positive (ER and PR negative, HER-2/neu positive), triple negative (ER, PR and HER-2/neu negative) or unknown. Results: Eight BRCA1 mutation carriers, 16 BRCA2 mutation carriers, and 51 non-carriers with pure DCIS were identified. Among BRCA1 carriers, 6 (75%) had luminal tumors, 1 (12%) had a triple negative tumor and in one case the phenotype was unknown. Among BRCA2 mutation carriers, 11 (69%) had luminal tumors and in 5 cases the phenotype was unknown. Among non-carriers, 36 (71%) had luminal tumors

and in 15 cases the phenotype was unknown. Conclusion: The majority of pure DCIS lesions in BRCA mutation carriers have a luminal phenotype. These data suggest that the emergence of the triple negative invasive phenotype in patients with BRCA1 mutations occurs at a late stage of tumorigenesis and may arise from a background of luminal DCIS.

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Molecular Alterations Associated with Early Breast Cancer Mortality R. Ellsworth,[1]* J. Campbell,[3] L. Voeghtly,[2] C.D. Shriver.[3] *1. Henry M. Jackson Foundation for the Advancement of Military Medicine, Windber, PA; 2. Windber Research Institute, Windber, PA; 3. Walter Reed Army Medical Center, Washington, DC.*

Background: Breast cancer is a highly heterogeneous disease and patients with otherwise similar pathologies treated with similar treatment regimens may have very different clinical outcomes. Identification of molecular alterations associated with disease outcome may serve as more accurate and non-subjective measures used to assess risk and prognosis as well as provide new molecular targets for improved treatment. Methods: A bank of allelic imbalance (AI) data representing 26 regions known to be frequently altered in breast cancer has been generated for >300 invasive breast tumors. A chart review was completed for patients diagnosed 2001 - 2005. Levels and patterns of AI were compared between patients who were dead of disease within 5 years of diagnosis (DOD) and those with long-term (>5 years) survival (LTS) using Student t-test and chi-square analysis with a significance value of $P<0.05$. Survival data was analyzed using GraphPad. Results: Levels of AI were significantly higher in tumors from the 24 DOD patients (26.9%) compared to the 70 LTS patients (20.9%). AI was found significantly more frequently in DOD tumors at chromosomes 7q31, 8p22-p21, 18q21 and 22q12.3 (26%, 45%, 33% and 38%, respectively) compared to LTS patients (4%, 14%, 13% and 13%). In contrast, chromosome 16q22-q24 was altered significantly less frequently in DOD (10%) compared to LTS tumors (40%). Survival analysis supported these findings for all but chromosome 22q12.3. Conclusion: Tumors associated with poor outcome are genetically more advanced. Alterations at chromosome 7q31, 8p22, 18q21 and 22q13 may be associated with increased risk of mortality, while loss of 16q appears to have a protective role. Research suggests that loss of the GINS2 gene (16q24), which is involved in the initiation of DNA replication, may protect against metastasis. These chromosomal regions and candidate genes may be effective targets for identifying patients with poor prognosis or serve as new targets for therapies to prevent or halt the metastatic process.

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Multi-lumen Partial Breast Irradiation with the SAVI Catheter E.C. Shieh, M.D.,[2]* B.H. Han, M.D.,[3] K. Imhoff, M.S., DABR,[1] P. Beck, A.S., CRC.[1] *1. South Florida Radiation Oncology, LLC, Wellington, FL; 2. South Florida Radiation Oncology, LLC, Port St. Lucie, FL; 3. South Florida Radiation Oncology, LLC, Boynton Beach, FL.*

PURPOSE: Several catheter-based devices are currently available for the delivery of PBI. We report our experience in utilizing the SAVI multi-lumen catheter in a multi-physician, multi-center setting. METHODS AND MATERIALS: Between January and December 2009, 75 consecutive women with newly diagnosed breast cancer elected to undergo breast-conserving therapy, including APBI with the SAVI ML breast catheter. 16 breast surgeons referred patients for radiation at one of 5 facilities. Eligibility criteria included women with either DCIS or invasive ductal carcinoma <3.0 cm, unifocal, with negative margins and lymph nodes. The patients underwent outpatient implantation of a SAVI ML catheter after final pathology was reviewed and eligibility confirmed. A pre-implant CT scan was performed to guide catheter sizing. A post-implant CT scan was utilized for treatment planning on the Nucletron Oncentra HDR planning system. 340 cGy was prescribed to a distance 1 cm beyond the catheter struts. We utilized multiple dwell positions to decrease skin and chest-wall dose where applicable. 10 treatments were delivered twice daily > 6 hours apart for a total dose of 3400 cGy. RESULTS: All women completed treatment without difficulty. Mean PTV was 77.6 cc (range: 32.3-187.9). Mean V90 was 92%. Mean V150 was 24.2. Mean V200 was 11.7 cc. Mean minimum skin distance was 13.4 mm (range 2-45). Mean % maximum skin dose was 66 (range 25-110). Mean rib distance was 21.2 mm (range 0-63). Mean % maximum rib dose was 61.6 (range12-123). At a mean f/u of 12 months (range 5-21), 74 of 75 patients are cNED. 1 patient has biopsy proven recurrence and underwent salvage mastectomy. She is now cNED. CONCLUSION: In this retrospective study, multi-lumen catheter high dose-rate brachytherapy with the SAVI device met the accepted criteria of treatment, was well tolerated, and shows excellent early local control, consistent with other methods of radiotherapy delivery. Long-term follow-up is necessary to assess local control and chronic local tissue effects.

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The Impact of Oncotype DX on Adjuvant Chemotherapy for Invasive Lobular Carcinoma J.L. Deneve,* M.C. Lee, J.E. Joh, G. Acs, N. Khakpour, H. Soliman, C. Laronga, J.V. Kiluk. *Surgical Oncology, Moffitt Cancer Center, Tampa, FL.*

Background: Indications for adjuvant chemotherapy in patients (pts) with early stage invasive lobular carcinoma (ILC) are ill-defined. Oncotype DX (ODX) testing is used to estimate risk of recurrence and guide adjuvant treatment for pts with early stage invasive ductal carcinoma. The impact of ODX testing in pts with ILC has not been reported. We investigate the impact of ODX testing on adjuvant chemotherapy use in node-negative ILC pts. Methods: An IRB-approved retrospective review was performed for pts with node-negative ILC from 1990-2011. Thirty cases of ILC with ODX were matched 1:1 based on tumor size (± 0.5 cm) and pt age (± 5 years) to a control group of ILC without ODX. Analysis was performed using t-test and chi square analyses. Results: Sixty pts (30-ODX, 30-Control) underwent treatment with a median age of 64 years (range, 41-77). ILC histology was classic (70%), pleomorphic (20%) and mixed/unknown (10%) with a median tumor size of 1.8 cm (range, 0.3-5.5 cm) for all pts. There was no statistical difference in patient age, ILC histologic type or median tumor size between groups. Intermediate tumor grade ($p=0.0001$) was higher in the ODX group. The median ODX recurrence score was 14.5 with 66% classified as low risk, 30% intermediate and 4% high risk for recurrence. Adjuvant chemotherapy was given to 23% in the ODX group and Control group, respectively. ($p=1.0$). Tumor size was larger for all pts who received chemotherapy (2.44 cm vs 1.59 cm, $p=0.031$). Comparing chemotherapy use between groups, there was no difference in tumor size (ODX 2.43 cm vs Control 2.45 cm, $p=0.97$) while high tumor grade trended towards statistical significance (ODX 29% vs Control 0%, $p=0.078$). With a median follow up of 21 months, there were 6 recurrences, all in the Control group, 4 of which were distant. Conclusion: ODX testing did not impact adjuvant chemotherapy use in pts with early stage ILC matched for tumor size and pt age. High tumor grade, although not significant, did however appear to impact chemotherapy use in pts who underwent ODX testing. ODX may allow better individual risk assessment when considering adjuvant chemotherapy for pts with early stage ILC.

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Tumor Size, Lymphovascular Invasion and Not Age as Predictive Factors for Axillary Lymph Node Metastases L.T. Greer,[2]* M. Rosman,[1] W. Mylander,[1] W. Liang,[1] R.R. Buras,[1] A.B. Chagpar,[3] M.J. Edwards,[4] L. Tafra.[1] *1. Breast Center, Anne Arundal Medical Center, Annapolis, MD; 2. Walter Reed National Military Medical Center, Bethesda, MD; 3. Smilow Cancer Hospital at Yale-New Haven, New Haven, CT; 4. University of Cincinnati, Cincinnati, OH.*

Introduction: Axillary lymph node (ALN) status at diagnosis is the most powerful prognostic tool for patients with breast cancer. Several nomograms calculate that the incidence of ALN metastases decreases with age. Recent data has contradicted this showing that the incidence of ALN metastases may increase in older women. Our aim is to review a large population treated at over 100 medical centers (with a large sampling of subjects >70) in order to examine the contribution of variables that lead to ALN metastases. Methods: Using two multicenter prospectively collected databases, a retrospective review was performed on 2,868 subjects diagnosed with invasive breast cancer from 1996 to 2005 who underwent ALN sampling. Variables including age at diagnosis, race, menopausal status, tumor size and location, mul-

tifocality/centricity, tumor type, histologic grade, presence of lymphovascular invasion (LVI), hormone receptor and lymph node status were collected. Multivariate logistic regression was used to identify variables that were independently associated with ALN metastases. Results: Of the 2,868 subjects with invasive breast cancer, 18% had ALN metastases at diagnosis. The incidence of ALN metastases is highest in young subjects after which it declines until age 60 and then begins to increase after 70. The proportion of patients with any positive ALN metastases is significantly higher in patients > 80 (23.5%, CI 18.0-30.1%) compared with those who are 60-74 (13.2%, CI 11.4-15.3%) years old. In reviewing the predictive factors, tumor size mirrored the shape of percent positive ALN across different ages (see Figure). Multivariate modeling reveals tumor size as the main factor driving the increased incidence of ALN metastases, and not age. LVI was also predictive, but all other factors were insignificant. Conclusions: The incidence of ALN metastases appears to increase after age 60. When all prognostic variables are examined, tumor size and LVI are driving the increase in ALN metastasis. All other variables were insignificant on multivariate analysis. The reason for these larger tumors in older women is open for speculation and warrants further investigation.

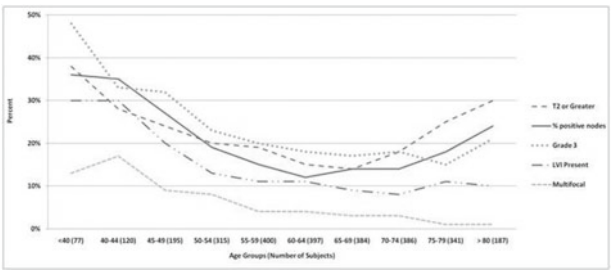

Figure 1: Age Groups versus Percent Predictive Factors. The percent of subjects with axillary lymph node metastasis is highest in young age groups with a decrease until age 70, after which it begins to increase. A similar phenomenon is seen in the tumor size over the age groups.

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Ductal Carcinoma In Situ, Low Rates of Recurrence Reduce the Significance of Conventional Prognostic Factors and Adjuvant Therapies D.Y. Lee,* R.E. Ross, J. Lewis, P.I. Tartter. *St. Luke's Roosevelt Hospital, New York, NY.*

Introduction The local recurrence rate for ductal carcinoma in situ (DCIS) treated with lumpectomy has declined considerably. This may reduce the significance of accepted prognostic factors and the need for adjuvant therapy. We studied patients with DCIS who were treated with breast conserving therapy (BCT), and evaluated the significance of prognostic factors and the effectiveness of adjuvant therapy. Methods A retrospective review of the database at our breast center was performed from 1987-2010, identifying all patients diagnosed with DCIS who had BCT. Patients with a concurrent diagnosis of invasive cancer were excluded. We examined the recurrence rate in relation to patient age, the Van Nuys Prognostic Index (VNPI), tumor size, nuclear grade, margins, hormone receptor status, and adjuvant therapy. Results We identified 479 patients with DCIS, and 294 met our inclusion criteria. Patient age, the VNPI, tumor size, nuclear grade, receptor status, and adjuvant use of radiation or Tamoxifen were not statistically significant in predicting recurrence (Table 1). Median follow up was 63 months with 6%(17) local recurrence rate. Three percent (7) developed invasive cancer. The average time to recurrence was 37 months. One patient treated with radiation and Tamoxifen recurred with lung metastases at 118 months. There were 11 deaths, none as a result of breast cancer. Overall, 67%(196) of the patients achieved margins ≥10mm, 25%(74) between 1-9mm, and 8%(24) <1mm. Re-excisions were performed in 55%(161) of the patients because margins were <1mm. In the re-excised population, 75%(121) had margins ≥10mm, 17%(28) between 1-9mm, and 7%(12) >1 mm. The relative risk of recurrence was 0.56 for margins ≥10mm and 1.78 for margins <10mm, but this did not reach statistical significance (p= 0.288). Conclusion We had a low recurrence rate, possibly due to the high rate of wide margins achieved by re-excisions. This suggests that in the setting of wide margins, conventional prognostic factors and adjuvant therapy for DCIS may be less significant. Re-excision should be performed when the margins are close, regardless of the plan for adjuvant therapy.

Table 1 - Characteristics of Patients with Recurrence versus No Recurrence

	Patients with Recurrence (n=17)	Percent	No recurrence (n=277)	Percent	p Value
Age (mean)	55.4 ± 15.7		56.7 ± 11.5		0.655
Race					0.388
Caucasian	13	76.5%	179	64.6%	
African American	4	23.5%	43	15.5%	
Hispanic	0	0.0%	42	15.2%	
Other	0	0.0%	13	4.7%	
Presentation					1
Clinical	2	11.8%	33	11.9%	
Mammographic	15	88.2%	242	88.1%	
Tumor Size (mean)	10.7 ± 18.6		8.3 ± 10.6		0.411
≤15mm	14	82.3%	233	84.1%	0.620
16-40mm	2	11.8%	36	13.0%	
≥41mm	1	5.9%	8	2.9%	
Nuclear Grade					0.684
Low	5	29.4%	60	21.7%	
Intermediate	7	41.2%	135	48.7%	
High	5	29.4%	82	29.6%	
Margin					0.330
≥10mm	9	52.9%	187	67.5%	
1 to 9mm	6	35.3%	68	24.6%	
<1mm	2	11.8%	22	7.9%	
Estrogen Receptor Positive	8	44.4%	146	52.7%	1.000
Received Radiation	8	47.1%	129	46.6%	1.000
Tamoxifen	6	35.3%	87	31.4%	0.790
VNPI(mean)	6.7 ± 1.6		6.4 ± 1.3		0.395

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WITHDRAWN

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Predicting Nipple-Areolar Involvement using Preoperative Breast MRI and Primary Tumor Characteristics S.T. Steen,* A.P. Chung, S. Han, A.L. Vinstein, J.L. Yoon, A.E. Giuliano. *John Wayne Cancer Institute, Santa Monica, CA.*

Introduction: Preoperative assessment of the nipple-areolar complex (NAC) is invaluable when considering nipple-sparing mastectomy (NSM). We hypothesized that breast MRI could predict involvement of the NAC with tumor. Methods: We compiled clinical, histopathologic and imaging data for patients who underwent preoperative breast MRI followed by mastectomy or NSM for malignancy between 2006 and 2009. Blinded rereview of all MRI studies was performed by a breast MRI imager and compared to initial MRI findings. Multivariate analysis identified variables predicting NAC involvement with tumor. Results: Of 77 breasts, 18 (23%) had tumor involving or within 1 cm of the NAC. The sensitivity of detecting histopathologically confirmed NAC involvement was 61% with history and/or physical exam, and 56% with MRI. Univariate analysis identified the following variables as significant for NAC involvement: large tumors close to the nipple on preoperative MRI, node-positive disease, invasive lobular carcinoma, advanced histopathologic T stage, and neoadjuvant chemotherapy. On multivariate analysis, only tumor size > 2 cm and distance to the NAC < 2 cm on MRI maintained significance. Pearson correlation coefficient for MRI size compared to histopathologic size was 0.53 ($p<0.0001$). Conclusion: MRI is not superior to thorough clinical evaluation

for predicting tumor in or near the NAC. However, MRI-measured tumor size and distance from the NAC are correlated with increased risk of NAC involvement. The combination of preoperative history and physical examination, tumor characteristics, and breast MRI can aid the surgeon in predicting for a tumor-involved nipple more than any single modality alone.

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Multi-frequency Bioimpedance Spectroscopy (BIS) for Detecting and Monitoring Patients for the Development of Upper Limb Lymphedema in the Clinic C. Shah,[1]* P. Whitworth,[2] D. Arthur,[3] F. Vicini,[1] M. Lyden.[4] *1. William Beaumont Hospital, Royal Oak, MI; 2. Nashville Breast Center, Nashville, TN; 3. Virginia Commonwealth University, Richmond, VA; 4. Biostat Inc., Tampa, FL.*

Introduction: With improvement in outcomes, chronic side effects of treatment including breast cancer related lymphedema (BCRL) are being recognized. Multi-frequency bioimpedance spectroscopy (BIS) has been used in clinical and research settings to measure extracellular fluid with its ease of use and low risk of user error suggests this assessment method may have advantages for use in community-based environments when compared to traditional methods. The purpose of this study was to evaluate multi-frequency bioimpedance BIS to detect and monitor BCRL and to assess its practicality on the clinical assessment of lymphedema. Methods: Using a standardized protocol, newly diagnosed breast cancer patients were evaluated with BIS at baseline and after surgery. The resulting sample consisted of 64 patients who underwent either mastectomy (n=13) or lumpectomy (n=51). L-Dex values were calculated prior to surgery and within 90 days following the completion of surgery. Results: Baseline values for all 64 patients ranged from -9.5 to 9.9 (median 0.5). When evaluating by axillary procedure, there was a trend for increased L-Dex values in patients receiving axillary lymph node dissection compared with sentinel node biopsy (3.4 vs. 1.3, p=0.08). This trend persisted when evaluating only those patients who underwent lumpectomy (3.0 v. 1.8, p=0.37). Further, when stratifying patients by number of lymph nodes removed, a trend for an increase in L-Dex values within 90 days of surgery was noted between those with four or more lymph nodes removed compared to those with less than four removed (2.6 vs. 1.2, p=0.09). This trend persisted when evaluating those patients who underwent breast-conserving therapy (2.7 vs. 1.5, p=0.19). Conclusions: These data support the continued use of BIS in the prospective management of women at risk for BCRL and warrants further studies evaluating the use of BIS to diagnose sub-clinical BCRL in patients. Further, studies are needed to help validate the extent, degree and chronological time-frame of these changes to help define recommendations for early intervention.

P110

Effect of Hormone Receptor Status on Rates of Breast Reconstruction A. Vijayasekaran, D. Summers, R. Viscusi, C. Hurst, A. Biswas, A. Waer, M. Ley, J.E. Lang.* *University of Arizona Department of Surgery, Tucson, AZ.*

Introduction: Disparities in breast reconstruction (BR) rates have been associated with age, race, geographical region (GGR) and radiation (XRT). We sought to investigate the relationship between estrogen receptor (ER) and progesterone receptor (PR) status and BR in the context of known covariates. Methods: The SEER (Surveillance, Epidemiology and End Results) database was used to evaluate breast cancer (BC) patients who underwent total mastectomy from 1998-2008. Age, race, GGR, lymph node (LN) status, grade, stage, ER/PR status, use of XRT and use of BR were recorded. Information regarding HER2 status and use of chemotherapy was not available in SEER. Univariate and multivariate analyses (MVA) were performed to study predictors of BR. Results: A total of 139,108 patients with BC were evaluated (15.9% had BR). BR significantly decreased as age increased ($p<0.0001$). Patients from the east had the highest likelihood of BR ($p<0.0001$). Patients with low grade disease (DZ) were 1.2 times more likely to have BR than the patients with high grade DZ ($p<0.0001$). Lower stage correlated with increased use of BR ($p<0.0001$). Our analysis included 73,057 (52.5 %) patients with 0; 40,212 (28.9 %) with 1-4; 12,232 (7.9 %) patients with 5-10; and 13,607 (10.7 %) patients with >10 positive nodes. On pairwise analysis of BR by LN status, fewer positive LNs predicted for BR ($p<0.0001$). 20.8% of the patients underwent XRT. The BR rate for patients not undergoing XRT was significantly higher than for those who underwent XRT ($p<0.0001$). ER+/PR+ patients had significantly higher BR rates when compared with ER-/ PR- patients ($p<0.0001$). The difference in BR between ER-/PR- patients and ER+ or PR+ patients was not significant ($p=0.12$). However, patients with stage I ER+/PR+ DZ were only 1.8 times more likely to have BR than patients with stage III ER-/PR- DZ. BR was found to be significantly associated with age, race, GGR, stage, ER, grade, LN status and XRT on MVA ($p<0.0001$), but not PR ($p=0.11$). Conclusion: BR correlated with age, race, GGR, stage, ER, grade, LN status, and XRT. ER but not PR status independently predicted for the use of BR after correcting for covariates such as XRT.

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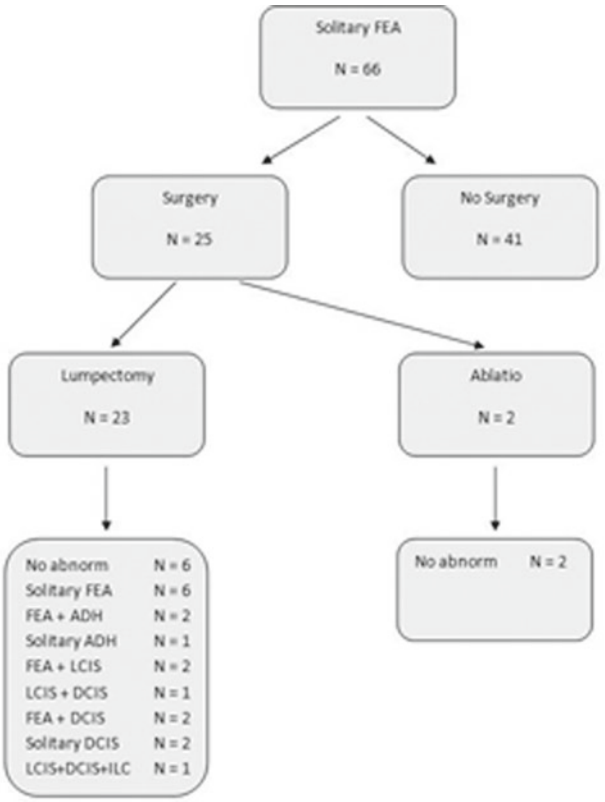
Flat Epithelial Atypia P. Ghuijs,[1]* C. Boetes,[1] F. Van der Ent,[2] K. Keymeulen,[1] M. Von Meyenfeldt,[1] L. Strobbe,[3] K. Van de Vijver,[1] C. Wauters,[3] M. Smidt.[1] *1. Maastricht Medical Hospital, Maastricht, Netherlands; 2. Orbis Medisch Concern, Sittard, Netherlands; 3. Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands.*

Background: Flat epithelial atypia (FEA) is a presumably neoplastic alteration of terminal duct-lobular units, characterized by replacement of native luminal epithelium by ductal cells, showing low-grade cytologic atypia and architectural stratification of epithelial cells. FEA is often accompanied by microcalcifications and thus discovered in biopsies following mammography. FEA can be accompanied with atypical ductal hyperplasia (ADH), low-grade ductal carcinoma in situ (DCIS), lobular neoplasia or invasive tubular carcinoma. Emerging evidence suggests FEA may be a precursor of DCIS, therefore, this risk should be defined. Detection of FEA in histological biopsy could be an indication for possibly present (pre-)malignant lesions. The aim of this study is to inventorise the consequences of solitary FEA in histological biopsies in three Dutch teaching hospitals. Materials and methods: Data of all FEA patients was retrospectively collected by searching local pathology databases for 'FEA', 'Flat Epithelial Atypia', and Dutch equivalents. Results were manually screened, including only solitary FEA. Patient files were viewed for information on presentation, imaging and chosen therapy (surgery vs follow-up). In case of excision, pathology results were added. Results: The search resulted in 161 cases, with 66 solitary FEA biopsies. Management consisted of follow-up for 41 patients (62%) and 25 (38%) underwent a lumpectomy (23) or mastectomy (2). No incidents occurred in the follow-up group so far. The definitive pathology of the excisions showed no abnormalities or solitary FEA in 6 patients each; other findings were ADH in 3, LCIS in 5 and DCIS in 6 patients. Invasive lobular disease (ILC) was only found in 1 patient. Reason for mastectomy was contralateral malignant disease; pathology showed no abnormalities. Conclusions: No consistent management exists concerning solitary FEA. DCIS or ILC was discovered in 24% of all surgical patients. Therefore, FEA can be seen as a red flag, indicating the possible presence of a more malignant lesion. Lack of this study is the retrospective gathering of data. Additional research is warranted, preferably as a multicentre randomized controlled trial comparing surgery vs follow-up.



P112

The Impact of Pathologic Step Sectioning on Sentinel Node Positivity and Intra-Operative Touch Preparation Cytology Accuracy in Breast Cancer K.M. Chambers,* E.J. Armstrong, III, B. Calhoun, T. Flippo-Morton, T. Sarantou, F. Greene, R.L. White, Jr.. *CMC, Charlotte, NC.*

Based on national guidelines, our institution changed its protocol for Sentinel Lymph Node (SLN) assessment in breast cancer patients in August of 2008 from intra-operative touch preparation cytology (IOTPC) with a single H&E-stained slide to IOTPC with two H&E-stained sections approximately 500 microns apart. We seek to determine the impact of this change on tumor detection in SLN analysis and the accuracy of IOTPC. Method: We compared two subsets; breast cancer patients who underwent sentinel node biopsy from 2006-2007 with those from 2009-2010, using retrospective review. Results: In 2006-2007, 602 cases (involving 589 patients) were performed. On final evaluation 141 of the 602 (23%) were positive for tumor. Of the positives: 65% had macroscopic metastasis and 25% microscopic metastasis (<2mm). 73 of the IOTPC evaluations were positive for tumor (52%). In 2006-2007, 8% of positive lymph nodes with microscopic disease were identified by IOTPC, as compared to 90% of those involved by macroscopic LN metastasis. In 2009-2010, 730 cases were performed. 160 cases were positive upon permanent pathology (22%), while IOTPC identified malignant involvement in 63 of the positive cases (39%). Of the positive lymph nodes identified by IOTPC, 92% had macroscopic metastasis while 8% had microscopic metastatic disease. In 2009-2010 53% of lymph nodes were positive for macroscopic disease on final path as opposed to 48% with micrometastasis (65% and 26% respectively in 2006-2007). The sensitivity of IOTPC in 2009-2010 (39%) as compared to 2006-2007 (52%) showed a statistically significant decrease ($p = 0.03$, Chi-square analysis). Conclusion: Analyzing lymph nodes with two H&E slides approximately 500 microns apart has led to an increased diagnosis of microscopic metastatic disease in sentinel lymph nodes, and a subsequent upstaging in breast cancer patients. The decreased incidence of macrometastases seen was associated with the decreased accuracy of IOTPC. The decreased incidence of macroscopic SLN in the latest cohort may be due to the increased utilization of preoperative axillary ultrasound and ultrasound guided node biopsy.

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Breast Conservation after Neoadjuvant Therapy for Large Tumors S. Libson,* V. Koshenkov, S. Rodgers, J. Hurley, E. Avisar. *Miller School of Medicine University of Miami, Miami, FL.*

Introduction: Neoadjuvant Therapy (NT) can facilitate breast conservation (BC). Similar oncologic outcomes have been reported with BC and mastectomy for large T2 lesions but studies of BC results for tumors >5cm are limited. Our experience with BC for tumors >5cm is reported. Patients and Methods: A retrospective analysis of a prospectively collected database of all breast cancer patients treated with NT at our institution between 2003-2010 was performed to identify patients treated with BC for tumors >5cm. Demographics, tumor histology, pathologic response, tumor margins, failure patterns and rates as well as survival rates were recorded. Results: Thirty two patients treated with BC after NT for large tumors were identified. The average follow up was 41 months and the mean age at diagnosis was 51.2. Pre/post menopausal rate was 17/15 (53%/47%). NT consisted of chemotherapy for 24(75%) patients and hormonal therapy for 8(25%). The average tumor size at diagnosis was 6.35cm. Tumor histology was ductal in 27(84%) patients and lobular in 5(16%). Estrogen receptors (ER) were positive in 17(53%) patients and Her2 was amplified in 8(25%). Eight patients (25%) underwent an oncoreductive procedure with concomitant reduction/lift of the contra-lateral breast. Negative margins were obtained at the first attempt in 31 patients (97%). One patient (3%) underwent a mastectomy for grossly positive margins. The average tumor size after surgery was 2.14cm. Post operative treatment consisted of radiation therapy for all patients, adjuvant chemotherapy for 6(19%) patients, hormonal therapy for the ER positive patients and Trastuzumab for the Her2 + patients. No local failure was noticed during the follow up period. Two patients (6%) had regional failure and only one patient (3%) had progression to systemic disease. The only patient who died of her disease had already systemic disease at diagnosis and her surgery was for local control only. Conclusion: BC after NT is a safe option for carefully selected patients with tumors >5cm. In this series, the oncologic results were comparable to those reported after mastectomy. Oncoplastic procedures enable more flexibility in the performance of BC.

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A Prospective Study Evaluating the Clinical Utility of Intraoperative Frozen Section Examination and Immunohistochemistry Evaluation of the Sentinel Lymph Node in the Setting of Prophylactic Mastectomy U.K. Ballehaninna,* V. Murthy, R.S. Chamberlain. *Saint Barnabas Medical Center, Livingston, NJ.*

Introduction: Prophylactic mastectomy (PM) is increasingly utilized as a breast cancer risk reduction strategy. When PM is performed, sentinel lymph node biopsy (SLNB) is often done to prevent the need for a formal axillary lymph node dissection (ALND) for axillary staging in the event an occult malignancy is detected. Intraoperative frozen section (IFS) and immunohistochemistry (IHC) evaluation of the SLN are typically performed on the SLN removed during PM, however few reports have addressed their validity in this setting. Materials/Methods: Clinico-pathologic data was prospectively collected from patients (2000-2011) who underwent PM and SLNB with IFS and IHC examination. Data was analyzed to determine the clinical significance of both IFS and IHC in the setting of PM and its impact on axillary management. Results: Among 292 women who underwent PM, 188 patients (64.5%) had SLN biopsy with IFS examination and IHC evaluation. Indications for PM was the presence of contralateral breast cancer (N=195, 66.7%), carcinoma in situ (N=53, 18.2%), strong family history (N=28, 9.6%), or BRCA 1 or 2 positivity (N=16, 5.5%). 375 SLNs were harvested (average 1.2, range 1-3). 4 patients (1.4%) were found to have carcinoma in–situ on final mastectomy pathology. No patient had invasive breast cancer. Only one of 188 patients (0.5%) had a SLN metastasis on IHC examination. IFS examination of SLN was negative in all 188 patients (100%) and IHC examination revealed no evidence of SLNM in 187 patients (99.5%). No patient required ALND. Conclusion: Despite increased adaptation of prophylactic mastectomy as a breast cancer reduction strategy; routine SLNB in this setting rarely identifies axillary metastases. IFS examination and IHC evaluation of the SLN in PM patients provides limited or no additional clinical information while significantly increasing operative costs and duration. Additional studies are needed to identify specific patient groups who may benefit from SLNB; however, IFS examination and IHC evaluation of the SLN in the PM setting can be safely excluded.

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Multidisciplinary Breast Conference Improves Patient Management and Treatment M.M. Blackwood,* S. Schaefer, E. Santoro, J. McDermott. *Surgery - Breast Health & Disease Management, St. Barnabas Medical Center, Livingston, NJ.*

Introduction: Few published studies have focused on the benefits of a multidisciplinary breast tumor board and its ability to impact patient management. A multidisciplinary breast conference that discusses the different clinicopathological aspects of the disease creates a sound, complete and unique treatment plan for each patient. The aim of this study is to highlight the role of weekly breast tumor boards in patient management and treatment modifications. Methods: From June 2010 to June 2011, 242 patients (Stage 0 to Stage 4 breast cancer) were prospectively presented before a multidiciplinary team at Saint Barnabas Medical Center (SBMC), beginning with clinical presentation, imaging and diagnosis followed by a prospective treatment plan formulated by the presenting physician. Following surgery, adjuvant treatment relevant to each patient was discussed. Due to SBMC's multiple campuses, each breast conference was performed via teleconference, which included video projection of pathology slides and images. Finally, feedback evaluations were distributed, completed and returned to the Tumor Registry for consistent weekly improvement of breast conference. Results: 102 patients (42%) had modified management after being presented at breast conference, of which 38% (n=39) were strictly surgical, 33% (n=34) medical treatment (chemotherapy/endocrine therapy), 17% (n=17) radiation, 6% (n=6) had changes to both medical and radiation treatment and 6% (n=6) resulted in imaging changes. Majority of changes were made to patients with Stage IA (27%) followed by patients with Stage 0 (21%) breast cancer. Conclusion: Breast conference has a significant impact on breast cancer patient management and treatment. Consultative discussion of each case permits each member of the breast cancer team to contribute to the development of the patient's treatment plan. This gives all physicians an opportunity to be aware of the patient's condition, background information as well as projected treatment plan, keeping a harmonious and cooperative breast cancer team along with best treatment option to the patient.

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Utility of a Prediction Model for Axillary Lymph Node Metastasis in Patients with Primary Breast Cancer using A Decision-tree Algorithm M. Takada,[1]* M. Sugimoto,[2] Y. Naito,[3] H. Moon,[4] W. Han,[4] D. Noh,[4] M. Kondo,[5] K. Kuroi,[6] H. Sasano,[7] T. Inamoto,[8] M. Tomita,[3] M. Toi.[1] *1. Department of Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 2. Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto University, Kyoto, Japan; 3. Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan; 4. Department of Surgery, Seoul National University College of Medicine, Seoul, Korea, Republic of; 5. Department of Health Care Policy and Management, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan; 6. Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; 7. Department of Pathology, Tohoku University Hospital and School of Medicine, Sendai, Japan; 8. Department of Breast Surgery, Tenri Hospital, Tenri, Japan.*

INTRODUCTION Information of axillary lymph node (AxLN) status affects the management of primary breast cancer. We have developed a mathematical model to predict AxLN metastasis in primary breast cancer patients using an alternating decision tree (ADTree) algorithm. The aim of this study was to evaluate the additional use of our model to a previous prediction model. METHODS An ADTree model was developed using a modeling dataset of 291 patients and an independent validation dataset of 174 patients with invasive breast cancer. Clinicopathological data before treatment were collected retrospectively from institutional databases. The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram for SLN metastasis was adapted to the validation dataset. The predictive accuracy of the combined use of the ADTree model and the MSKCC nomogram was evaluated. RESULTS The ADTree model developed with 15 variables showed accuracy with the area under the receiver operating characteristics curve (AUC) values 0.770 in the modeling dataset and 0.772 in the validation dataset, respectively. The nomogram showed accuracy with AUC values 0.713 (95%CI, 0.621 – 0.805) in the validation dataset and could discriminate patients with positive AxLN and negative AxLN at statistically significant levels ($p<0.0001$). When patients with predictive values of 50% or less were defined as low-risk of AxLN metastasis, the false negative rate (FNR) was 33.3% in the ADTree model and 53.8% in the nomogram, respectively. The combination of the ADTree model and the nomogram showed FNR of 39.1% and assigned 57.1% of patients to the low-risk group. When patients with predictive values of 30% or less were defined as low-risk of AxLN metastasis, FNR was 17.9% in each model. The combination of the ADTree model and the nomogram showed FNR of 9.7% and assigned 28.6% of patients to the low-risk group. CONCLUSIONS Employment of our model after the prediction of the nomogram improved predictive accuracy. However, our model requires more variables compared to the previous models. To improve usability of our model we have developed some software which is available on our website.

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Effect of Surgery on Overall Survival in Breast Cancer Patients Aged >80 Years A. Perhavec,* B. Peric, G. Pilko, R. Petric, M. Hocevar, J. Zgajnar, N. Besic. *Department of surgical oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia.*

Background As the population ages, the proportion of breast cancer pts aged >80 years is increasing. The data show that these pts are undertreated, often receiving hormonal therapy only. The aim of our study was to ascertain whether surgical therapy has a survival advantage over other treatment modalities in breast cancer pts aged >80 years. Patients and methods Clinical records of 221 early breast cancer pts aged >80 years that started treatment at our institute from January 2000 to December 2004 were analysed. Mean age was 84.4 (range 80.1 - 98.8). Cox regression model was used to determine the influence of surgical therapy on overall survival. Other covariates included in the model were age, ASA value (physical status classification system), WHO performance status, tumor and nodal stage. Results Surgical therapy (S), radiotherapy (RT), hormonal therapy (HT) and chemotherapy (CT) were used in 72, 23, 212 and 5 pts, respecitvely. Surgical therapy only, HT only, RT only, combination of S+HT, S+RT, S+HT+RT, S+CT+HT, RT+HT, CT+HT and CT+HT+RT were used in 6, 134, 2, 56, 1, 8, 1, 9, 1 and 3 pts, respectively. Surgery was initial treatment in 54 pts, while 18 pts were surgically treated after preoperative therapy. Of those who received HT as initial therapy, 26% progressed, 34% had stable disease, 18% had partial and 22% had complete response to HT. Median survival of all 221 pts was 41 months and of those who had surgery as initial therapy, surgery after preoperative therapy and no surgery it was 83, 57 and 33 months, respectively. In multivariant Cox regression model four variables significantly predicted overall survival: surgical therapy (HR [95% CI]: 2.5 [1.6-3.9], $p<0.001$), age (HR [95% CI]: 1.071 [1.02-1.12], $p=0.005$), tumor stage (HR [95% CI]: 1.19 [1.01-1.4], $p<0.037$) and nodal stage (HR [95% CI]: 1.31 [1.01-1.69], $p<0.041$). ASA value and WHO perfomance status were not significant. Conclusion Surgical therapy seems to be a better option for management breast cancer pts aged >80 years in comparison to conservative therapy. Despite possible selection bias our retrospective study shows that surgery should be performed whenever possible in these subgroup of breast cancer pts.

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Value of the Pre-treatment Albumin to Globulin Ratio in Predicting Long-term Mortality in Breast Cancer Patients B. Azab,* S. Vonfrolio, V.R. Bhatt, A. Habeshy, J. Patel, A.I. Picon, S. Bloom. *Surgery, Staten Island University Hospital, Staten Island, NY.*

Background: Prior studies demonstrated the prognostic value of pretreatment serum albumin concentration in different types of cancer. Moreover, a study used serum protein electrophoresis found significantly higher globulin but lower albumin concentration and albumin globulin ratio (AGR) in cancer patients compared to normal persons after adjusting for other confounding variables. Our aim in this study was to explore the value of pretreatment AGR to predict the long-term mortality in breast cancer

patients. Methods: Our observational study used an unselected cohort of breast cancer patients treated at community tertiary center between January 2004 and December 2006. A total of 354 patients had a total protein, albumin and calculated AGR obtained prior chemotherapy. Survival status was obtained from our cancer registry and social security death index. Survival analysis, stratified by AGR tertiles, was used to evaluate the predictive value of AGR. Results: Patients in the highest AGR tertiles (AGR>1.45) had lower 5-year (7/116=6% vs. 22/121=18% vs. 37/117=32%) mortality rate compared to those in the middle (AGR 1.21-1.45) and the lowest (AGR<1.21) tertiles (p 0.0005 and <0.0001, respectively). After exclusion of the patients died in the first 2-month of the follow-up period and those with albumin <3.6, AGR remained a significant predictor of survival (p<0.0001 and 0.0018, respectively). In a multivariate model including AGR, AJCC stage and patient age, the AGR remained an independent significant predictor of 5-year mortality [Hazard ratio per unit increase of AGR decreases by 0.168, 95% confidence interval 0.07-0.39, p=0.0001] [Hazard ratio of AGR<1.21 vs. AGR>1.45 was 4.1, p=0.0002]. Conclusion: Pretreatment AGR is a significant predictor of long-term mortality in the breast cancer patients even among those with normal albumin concentration and after adjusting for the age and the cancer stage. We suggest larger prospective studies to evaluate the AGR as a simple prognostic test for breast cancer.

The 5-year all-cause mortality according to the pretreatment albumin globulin ratio (AGR) in the breast cancer patients.

	5-Y mortality in the total study population	5-Y Mortality in the post-2-M survivors*	5-Y Mortality in patients with albumin>3.5gm/dl
AGR tertiles	1st vs. 3rd tertile p<0.0001	1st vs. 3rd tertile p<0.0001	1st vs. 3rd tertile p=0.0018
AGR <1.21	37/117(31.6%)	29/109(26.6%)	10/51(19.6%)
AGR 1.21-1.45	22/121(18.2%)	21/118(17.8%)	15/94(15.6%)
AGR>1.45	7/116(6.0%)	7/116(6.0%)	4/109(3.7%)

P values are according to two-tailed Fisher's exact test.(*) analysis including only patients who survived after 2-month of blood collection.

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The Value of the Pretreatment Hematological Biomarkers in Predicting Long-term Survival in Breast Cancer B. Azab,* S. Vonfrolio, V.R. Bhatt, A. Habeshy, J. Patel, A.I. Picon, S. Bloom. *Surgery, Staten Island University Hospital, Staten Island, NY.*

Background: Prior studies demonstrated the association of the hematological parameters [e.g. white cell subtypes, neutrophil-to-lymphocyte ratio (NLR)and platelet lymphocyte ratio (PLR)] and the survival in cancer populations. The aim of this study was to determine if these pretreatment hematological biomarkers are predictors of the long-term survival in breast cancer patients. Method: Our observational study used a total of 437 unselected cohort of breast cancer patients who had complete blood count recorded prior to chemotherapy treatment, between January 2004 and December 2006. Survival status was obtained from our cancer registry and social security death index. Using NLR, PLR, Platelet, neutrophil, and lymphocyte quartile models, we ran survival analyses to evaluate their predictive value in regards to 5-year all-cause mortality. We ran additional survival analyses excluding the all the patients died within 2 months of the recorded hemogram (post-2-month survivors). Results: The lowest neutrophil (<3.5), NLR (<1.8) and PLR (<109) quartiles and the highest lymphocyte (>2.2) quartile had significant lower 5-year mortality rates compared to the highest neutrophil (>5.6), NLR (>3.2)and PLR (>184) quartiles and the lowest lymphocyte (<1.5) quartile (9.5% vs. 36.7%, 7.4% vs. 40.3%, 11.0% vs. 30.4% and 10.3% vs. 34.5%, respectively with p<0.001) (table 1). Similar statistical significant results were obtained after exclusion of those died within 2-month of start point (table 1). After adjusting for the age and AJCC stage, the neutrophil, lymphocyte, NLR and PLR were independent predictors of 5-year mortality. Conclusion: The lymphocyte, neutrophil, NLR and PLR are significant predictors of long-term mortality in breast cancer patients even after adjusting for age and cancer stage. Further studies are needed to confirm these findings and explore the underlying mechanisms.

Table 1. Mortality rates according to the pretreatment hematological variables.

	5-Y Mortality in the total study population	5-Y Mortality in the post-2-M survivors*
Neutrophil (N) quartiles	1st vs. 4th N quartile, p<0.0001	1st vs. 4th N quartile, p<0.0001
N <3.5	10/105(9.5%)	10/105(9.5%)
N 3.5-4.4	13/114(11.4%)	12/109(11.0%)
N 4.5-5.6	11/109(10.1%)	10/107(9.3%)
N>5.6	40/109(36.7%)	32/100(32.0%)
Lymphocyte (L) quartiles	1st vs. 4th L quartile, p<0.0001	1st vs. 4th L quartile, p<0.0001
L<1.5	39/113(34.5%)	32/105(30.5%)
L 1.5-1.8	15/114(13.2%)	13/109(11.9%)
L 1.9-2.2	8/93(8.6%)	8/91(8.8%)
L>2.2	12/117(10.3%)	11/116(9.5%)
NLR quartiles	1st vs. 4th NLR quartile, p<0.0001	1st vs. 4th NLR quartile, p<0.0001
NLR<1.8	8/108(7.4%)	8/104(7.7%)
NLR 1.8-2.3	9/106(8.5%)	9/103(8.7%)
NLR 2.4-3.2	9/108(8.3%)	9/108(8.3%)
NLR>3.2	48/119(40.3%)	38/106(35.8%)
Platelets (P) quartiles	1st vs. 4th P quartile, p=0.1179	1st vs. 4th P quartile, p=0.0220
P<223	16/114(14.0%)	10/106(9.4%)
P223-260	16/108(14.8%)	15/104(14.4%)
P261-306	18/108(16.7%)	17/106(16.0%)
P>306	24/107(22.4%)	22/105(22.0%)
PLR quartiles	1st vs. 4th PLR quartile, p=0.0004	1st vs. 4th PLR quartile, p=0.0003
PLR<109	12/109(11.0%)	9/105(8.6%)
PLR 109-138	13/106(12.3%)	13/103(12.6%)
PLR 139-184	14/107(13.1%)	12/104(11.5%)
PLR >184	35/115(30.4%)	30/109(27.5%)

(*)= Exclusively, the patients who survived 2 months after laboratory data collection. P values were calculated according to the two-tailed exact Fisher's test.

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High Survivin Expression in Ductal Carcinoma In Situ (DCIS): A Potential Therapeutic Target H.L. Graves,* R. Mick, A. Sharma, R. Lewis, S. Roberts, E. Fitzpatrick, S. Xu, B. Czerniecki, P. Zhang. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Survivin, a member of the Inhibitor of Apoptosis Proteins (IAP), is involved in cell proliferation, apoptosis suppression, and angiogenesis. Survivin is highly expressed in many cancers, including invasive breast cancer, and its expression is often correlated with more aggressive disease and poorer outcomes. Our goal was to characterize survivin expression in ductal carcinoma in situ (DCIS) with a specific interest in correlation to histopathologic grade and hormone receptor (HR) status. Methods: Immunohistochemistry was performed on paraffin-embedded tissue containing DCIS (n = 93). Survivin expression was evaluated for intensity (1-3+) as well the percentage of tumor staining (0-100%). A numerical score was calculated by multiplying the intensity by percentage staining giving an overall score from 0 to 300. Immunoreactivity was scored separately for the cytoplasm and nuclei. Results: Cytoplasmic survivin expression was found in 91/93 (97.8%) DCIS patients, with 78/91 (85.7%) positive patients showing a score of 100 or greater, suggesting cytoplasmic survivin plays a role in early breast cancer survival. There was a positive correlation between cytoplasmic survivin expression and histopathologic grade. Median cytoplasmic survivin scores were 110, 170, and 222.5 for low (n = 11), intermediate (n = 34), and high grade (n = 48) DCIS (Spearman rank correlation, r = 0.47; p < 0.001). Figure 1 shows concurrent high and low grade DCIS with differential survivin staining. There was no correlation between histopathologic grade and nuclear survivin levels. HR positive DCIS showed higher levels of nuclear survivin than HR negative DCIS (p = 0.02), while HER2 positive DCIS showed lower levels of nuclear expression than HER2 negative DCIS (p = 0.04). There was no correlation between HR and HER2 status and cytoplasmic survivin. Conclusion: Increasing levels of cytoplasmic survivin appear to correlate with higher histopathologic grade and aggressiveness. Nuclear survivin levels appear to correlate with HR positivity. Due to its high level of expression in DCIS, survivin is an excellent therapeutic target for treatment and prevention of early breast cancer.

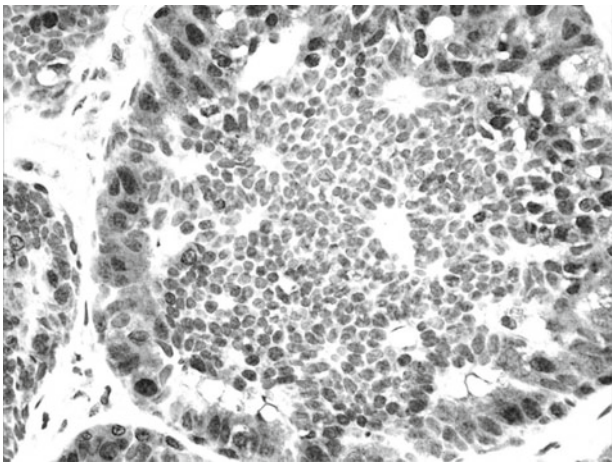

Figure 1 shows concurrent low and high grade ductal carcinoma in situ (DCIS) at 20x magnification. The high grade tumor in the periphery shows intense survivin staining while the low grade tumor in the center shows no survivin staining.

Factors associated with lack of treatment for breast cancer

Factor	Univariate Analysis		Multivariate Analysis	
	N (%)	p value	OR (95% CI)	p value
Race Caucasian African-American Asian	6(10.7%) 4 (1.3%) 5 (3.5%)	0.294	Referent 0.51 (0.05-5.45) 0.63 (0.04-11.09)	0.835
Age < 50 50-60 > 60	2(6.0%) 3 (1.5%) 12(4.2%)	0.202	Referent 0.08 (0.01-1.01) 0.03 (<0.01-0.37)	0.024
Education < grade 12 High school grad Some college University degree	6 (10%) 4 (1.3%) 5 (4.1%) 2 (5.6%)	0.003	2.39 (0.52-11.03) 0.28 (0.04-1.93) 1.21 (0.15-9.67) Referent	0.174
Insurance Not covered Medicare/Medicaid/Military Private	0 (0%) 16(5.5%) 1 (1.8%)	0.009	-- 24.70 (3.88-170.30) Referent	0.001
Region Northeast Midwest South West	7(10.6%) 1 (1.0%) 4 (2.9%) 5 (3.4%)	0.031	21.62 (1.07-437.80) Referent 5.13 (0.27-98..42) 5.10 (0.34-76.18)	0.149
Perceived risk High risk Average risk Low risk	10(4.9%) 2 (1.0%) 4 (4.1%)	0.075	1.44 (0.40-5.20) 0.15 (0.03-0.65) Referent	0.002

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Factors Associated with Lack of Breast Cancer Treatment
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Introduction: Breast cancer is a highly curable disease when discovered early and treated appropriately; yet some women in the United States are not receiving treatment for this disease. We sought to determine the sociodemographic and patient related factors associated with lack of treatment for breast cancer in a population-based cohort. **Methods:** The National Health Interview Survey (NHIS) is conducted annually by the Centers for Disease Control and is designed to collect health related information that is representative of the American population. The 2010 data release was queried, and factors associated with breast cancer treatment (or lack thereof) were determined. Statistical analyses were performed using SUDAAN software and variances were derived for the larger population-based cohort. **Results:** In 2010, 387 people with a history of breast cancer were surveyed, representing 2,764,854 individuals in the population. Of these, 17 (3.95%) reported receiving no treatment; this represented 96,536 individuals in the population. Factors associated with receiving no treatment included education (p=0.003), insurance status (p=0.009), and region of residence (p=0.031). There was a trend for those at higher perceived risk to receive no treatment for their breast cancer (p=0.075). Age and race, however, did not affect whether breast cancer patients received treatment (p=0.202 and 0.294, respectively). On multivariate analysis, insurance status (p=0.001), perceived risk of breast cancer (p=0.002), and age (p=0.024) were significantly associated with receipt of treatment. **Conclusion:** Nearly 4% of patients with breast cancer do not receive any treatment for their disease. Young patients and those without private insurance are a particularly vulnerable population warranting public attention.

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Upstaging after Surgical Excisional Biopsy of High Risk Breast Lesions Identified by Core Needle Biopsy
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Background: The role of surgical excisional biopsy of high risk breast lesions remains controversial. High risk lesions include atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), flat epithelial atypia (FEA), lobular carcinoma in situ (LCIS), and papillary lesions with and without atypia. The aim of this study was to evaluate the frequency of a final diagnosis of malignancy in patients with a core biopsy demonstrating a high risk lesion. Methods: With IRB approval, using a prospective surgical database, we identified all patients with a preoperative core biopsy diagnosis of ADH, ALH, FEA, LCIS, and papillary lesions with and without atypia that had surgical excisional biopsy at our institution between October 2008 and July 2011. In our practice, ADH and papilloma with atypia are routinely excised and other lesions undergo excision selectively. Cases with known concomitant ipsilateral cancer were excluded. Final pathology results were analyzed to determine frequency of upstaging to carcinoma at time of excisional biopsy. Results: Of the 287 excisional biopsies for high risk lesions identified in 280 patients, preoperative diagnoses included 174 ADH, 52 ALH, 19 FEA, 14 LCIS, 15 papillary lesions without atypia, and 13 papillary lesions with atypia. The upstage rate to ductal carcinoma in situ (DCIS) or invasive cancer after excisional biopsy was 14% for ADH (25/174), 7% for LCIS (1/14), 6% for ALH (3/52), and 0% for FEA (0/19). Papillary lesions with atypia were upstaged in 3 of 13 cases (23%), and no papillary lesions without atypia were upstaged. Of the 32 malignancies identified, 27 (84%) were DCIS and 5 were invasive cancer (2 upstaged from ADH, 2 from ALH and 1 from LCIS). Conclusions: In patients undergoing routine surgical excision of ADH and papillary lesions with atypia, coexistent malignancy is identified in 14-23% of cases. At the time of selective surgical excision of ALH and LCIS, malignancy is less commonly encountered. FEA and papillary lesions without atypia were not associated with malignancy in this small series.

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Factors Influencing Surgical and Adjuvant Therapy in Stage I Breast Cancer
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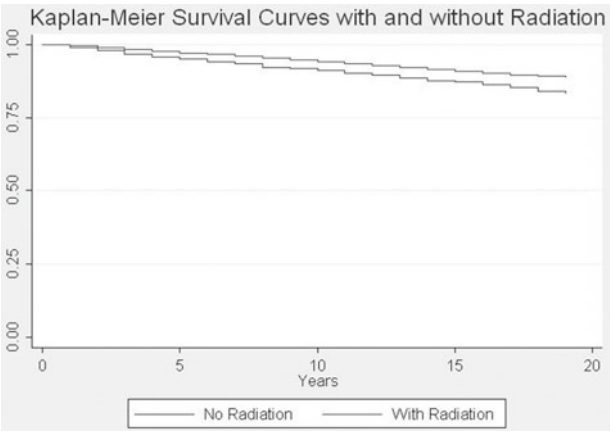
Introduction: Randomized clinical trials have shown no survival difference for patients with stage I breast cancer who are treated with mastectomy versus breast conserving surgery (BCS) with adjuvant radiation therapy (RT). Clinical guidelines recommend the use of RT for patients who choose BCS, in order

to decrease local recurrence and mortality. We sought to determine potential factors that resulted in patients receiving mastectomy or BCS. We then evaluated for any factors that influence the use of RT after BCS. Methods: We identified 194,860 women with stage I breast cancer diagnosed between 1988 and 2007 using the Surveillance, Epidemiology, and End Results (SEER) data. Results: From 1988-2007, the rate of mastectomy decreased over time from 60% in the first 5 years of the study period to 32% in the last 5 years. Significant predictors for being treated with mastectomy rather than BCS on multivariate analysis included single/divorced women (p= 0.007), Caucasian race (p<0.001), estrogen receptor (ER) negativity (p<0.001) and earlier year of diagnosis (p<0.001). Factors that were not predictive of surgical treatment included age, tumor size, mean income and mean education level. Despite known benefit from RT, 20% the patients treated with BCS did not receive RT. The rate of RT in patients treated with BCS did not change over time (19% in the first 5 years and 21% in the last 5 years). Significant predictors for not receiving RT on multivariate analysis included small tumor size (p<0.001), African American race (p<0.001), increasing age (p<0.001), single/divorced women (p<0.001), and ER negativity (p<0.001). Factors that did not predict for the use of adjuvant RT included age, mean income and mean education level. Cox regression analysis showed that the survival for patients treated with BCS and RT was significantly higher than for those patients who had BCS and no RT (HR 0.61, p<0.001). Conclusions: The use of BCS for the treatment of stage I breast cancer increased over time. There were a proportion of patients who do not receive RT after BCS; this has been stable over the last two decades. Omission of RT in BCS is associated with an increase in mortality.



Kaplan-Meier Survival Curve: Patients Treated with Breast Conserving Surgery with and without Adjuvant Radiation Therapy.

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Impact of Inappropriate Genetic Testing on Patients with Breast Cancer K. Massimino,[1]* P.B. Dorsey,[2] M. Glissmeyer,[2] G. Anadiotis,[2] N.G. Johnson.[2] *1. Surgery, Oregon Health & Science University, Portland, OR; 2. Legacy Cancer Services, Portland, OR.*

Background: BRCA1 and BRCA2 mutations account for 65% of the breast cancers due to a hereditary mutation. Rapid testing for these mutations is available and is being utilized by physicians for patients with newly diagnosed breast cancer to guide surgical therapy without referral for formal genetics evaluation. The impact of improperly ordered genetic tests is unknown. Methods: Over a one year time period, patients in whom BRCA testing was ordered prior to meeting with a genetic counselor in a risk assessment program were identified. These cases were reviewed with respect to completeness of family history evaluation, appropriateness of initial genetic testing and impact of results on disease management and patient counseling. Results: One-hundred one patients were seen for genetic counseling related to hereditary breast cancer in the included time period. Nine patients (9%) had BRCA testing ordered prior to genetic counseling. All patients had negative results. The majority of tests (67%) were ordered by surgeons. In five of nine patients (56%) this was an inappropriate initial genetic test. Three of these patients subsequently completed the appropriate testing while 2 (40%) did not. Of the 4 patients in whom BRCA was the appropriate initial test, two refused additional recommended testing after a negative BRCA result. All patients had significant family history of cancer that was not initially extracted at their physician visit prior to BRCA testing. In total, six patients needed additional testing for other causes of hereditary cancer including Lynch syndrome, Cowden's syndrome, CHEK2 mutation and the Adenomatous Polyposis Coli I1307K gene. Four of six patients (67%) did not complete this testing. Cost of additional testing was a factor. Conclusions: Formal genetic counseling may better serve patients in whom a hereditary cause of cancer is suspected. If BRCA testing is expedited for surgical management reasons, a thorough family history should be obtained prior to test selection. In addition, patients should understand that negative results do not always obviate the need for additional genetic study.

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What is the Relationship between Abdominal Fat Volume Measurements and Angiolymphatic Invasion in Breast Cancer Patients? C. Onwubiko, H. Zhang, R. Crowell, M. Griswold, A. Smith, L. Miele, S. Patterson.* *University of Mississippi, Jackson, MS.*

Introduction: Angiolymphatic invasion (ALI) is a pathology-based tumor characteristic associated with a poor prognosis in breast cancer (BC) that has been shown to be closely associated with increases in body mass index (BMI). Fat compartments can be directly quantified using anatomic landmarks and body fat attenuation characteristics on CT scans that are routinely obtained for staging of BC patients. This study proposes that increased amounts of fat are strongly associated with the presence of ALI. Methods: A retrospective review was performed of all BC patients from 2005-2010 who received staging CT scans within six months of diagnosis. Radiologists (blinded to pathology and clinical outcome) quantified the volume of body fat (total (TAF), subcutaneous (SAF), and visceral (VAF)) in the abdominal compartments. Linear regression models were used to describe the relationship between ALI and predictors. We used approximate standard deviations in reporting regression coefficients to have comparable contrasts between BMI (1 kg/m2) and SAF (400cc3). Results: 267 patients were included in this study. Most patients had ductal carcinoma (n=227, 85.02%) and African American (n=169, 63.30%) . 34.83% of patients were found to have ALI on histology. The groups were similar in age (Table 1). In patients with ALI, the average SAF was higher than patients not found to have ALI. SAF was more closely associated with the presence of ALI than BMI. VAF was not closely associated with the presence of ALI. For an increase of 1 unit in BMI, the odds ratio for ALI was 1.02 (95%CI 0.99, 1.05) while an increase of 400cc3 in SAF resulted in an odds ratio of 1.29 (95%CI 1.01, 1.66) which approaches statistical significance. Increasing pathologic size and clinical stage were closely related to the presence of ALI (p<0.0001). Conclusion: SAF volume as measured by CT is strongly associated with a higher incidence of ALI in breast cancer patients. This association is stronger than that found with BMI. SAF is more prognostic of this adverse feature than VAF. Additional information from these routinely obtained CT scans can offer additional prognostic information.

Table 1: Study Group Characteristics

	Total n = 267	No ALI n = 174	ALI n = 93	p-value
Age at Diagnosis	53.32	52.77	54.34	0.48
Triple Negative Histology	n=64 23.97%	n=42 24.14%	n=22 23.66%	1.00
Average BMI	32.09	31.63	32.97	0.14
Visceral Abdominal Fat VAF(cc3)	335.15	336.53	332.59	0.75
Subcutaneous Abdominal Fat SAF(cc3)	813.93	775.76	883.91	0.07
Total Abdominal Fat TAF (cc3)	1169.84	1127.41	1248.10	0.10

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Early Operative Experience with Targeted Intraoperative Radiotherapy using the Intrabeam Delivery System J.L. Deneve,* M.C. Lee, N. Khakpour, J.V. Kiluk, E.E. Harris, C. Laronga. *Surgical Oncology, Moffitt Cancer Center, Tampa, FL.*

Background: Targeted intraoperative radiotherapy (IORT) as an alternative to whole breast irradiation (WBI) has been described for early breast cancer. The Intrabeam delivery system demonstrated similar recurrence to WBI with a lower toxicity profile on short-term follow up. Recently introduced in the United States, we report on our early surgical experience using the Intrabeam radiotherapy delivery system. Methods: Prospectively gathered ER-positive, clinically node-negative patients (pts) with invasive breast cancer <3 cm receiving IORT using Intrabeam were reviewed after IRB approval. IORT-related effects and early post-operative outcome were assessed. Results: Twenty-eight pts (median age 72.5 yrs) underwent lumpectomy, sentinel lymph node biopsy (SLN) and concurrent IORT from 1/2011-7/2011. Ninety-three % of pts had invasive ductal histology with median tumor size of 0.95 cm (range 0.2-2.0). Subcutaneous tissue flaps were created in 68% to achieve skin-to-applicator distance >1 cm. IORT was delivered using a 3cm (79%) or 3.5cm (21%) applicator. All pts received 20 Gy IORT administered over a median duration of 25 minutes (range 15-25) with median operative time of 123 minutes (range 90-153). Seven pts (28%) had close (<2 mm) or positive microscopic margins after treatment, for which 6 had re-excision. A negative microscopic final margin (>2 mm) was obtained in 96%. Three pts (11%) received additional WBI (close final margin with (+) SLN N=1, (+) SLN on IHC without ALND N=2), 11% received adjuvant chemotherapy. Physical exam findings at 1st post-operative follow up included: localized IORT-related hyperemia (46%), asymptomatic seroma (29%), and cellulitis (7%). The one pt with cellulitis required operative abscess drainage. Four pts received planned 6 month post-IORT breast ultrasound; 2 had evidence of an asymptomatic seroma. Conclusion: Early operative experience with IORT is well tolerated with low morbidity. Delivery of IORT adds moderate operative time, and may require creating subcutaneous tissue flaps. The addition of WBI may be necessary for positive residual margins or microscopic nodal disease in pts who do not undergo additional surgery.

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Subcutaneous Abdominal Fat rather than BMI Correlates with Residual Cancer Burden S. Tanner, A. Brown, H. Zhang, A. Smith, C. Onwubiko, M. Griswold, L. Miele, S. Patterson.* *University of Mississippi, Jackson, MS.*

INTRODUCTION: Pathologic complete response to neoadjuvant cytotoxic chemotherapy (NAC) is decreased in obese breast cancer (BC) patients. The residual cancer burden (RCB) calculator is useful in quantifying the levels of response to NAC. We propose obesity as measured by amount of adipose tissue on CT scan as a prognostic tool in RCB. METHODS: A retrospective chart review identified BC patients who underwent NAC and had a CT scan obtained for staging purposes within 6 months of diagnosis from 2005-2010. These CT scans were analyzed to calculate the amount of adipose tissue in the abdomen (Figure 1). Pathologic slides from the definitive surgery were reviewed and the RCB was calculated using the MD Anderson RCB calculator. Clinical information was obtained from the clinical chart. Linear regression models were used to describe relationships between RCB scores and predictors. We used approximate standard deviations in reporting regression coefficients to have comparable contrasts between BMI (5 kg/m2) & subcutaneous abdominal fat (SAF) (500 ccq increase). RESULTS: 56 patients were included in this study (38 AA, 18 Caucasian). 19 were triple negative tumors. Average age at diagnosis was 50.84 (29-73). 49 patients had a mastectomy and 7 had breast conservation surgery. All patients had either a sentinel lymph node biopsy (n=7), axillary dissection (n=46), or both (n=3). The average BMI was 31.28 (18.10-45.70). Most patients were clinical Stage 3 (54.72%). Regarding RCB, 16 (30.19%) were RCB Class 2, and 38 (69.81%) were RCB Class 3. The average amount of SAF was 881.94 (154.10-1938.90). A 500 cc3 increase in SAF was associated with a statistically significant 0.38 (95% CI: 0.04, 0.72) increase in RCB score (p=0.030), while there was no evidence of a relationship between BMI and RCB; a 5 unit increase in BMI had an estimated association of 0.12 (-0.09, 0.32, p=0.254)(Figure 1). CONCLUSION: CT scans are routinely utilized in treatment planning of BC prior to administering NAC. Our data suggest that quantification of adipose tissue using CT scans may have more prognostic utility than BMI in BC patients receiving NAC.

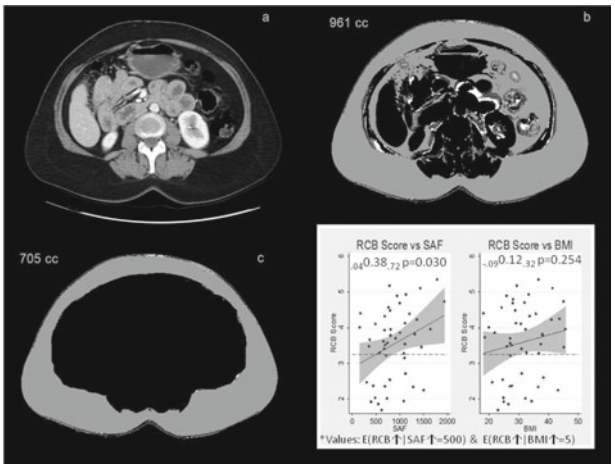

Figure 1: Measurement of abdominal fat volumes.[A] Standard axial CT image [B] Total Abdominal Fat (961cc3) and [C] Subcutaneous Abdominal Fat (705cc3) volumes.[D] Estimated probabilities from logistic regression models with confidence bands shown along with odds ratio (OR), related to 95% confidence intervals for Subcutaneous Abdominal Fat (SAF) and Body Mass Index (BMI). Displayed as lower 95%CI OR upper 95% CI. The red line indicates the Residual Cancer Burden (RCB) score that divides RCB Class 2 (below the line) and RCB Class III (above the red line).

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Feasibility of 3D Intraoperative Freehand SPECT Probe Imaging for Radio-guided Tumor Excision and Sentinel Node Biopsy in Breast Cancer O.R. Brouwer,* J. Van der Hage, F.W. Van Leeuwen, R.A. Valdés Olmos. *Nuclear Medicine / Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Noord Holland, Netherlands.*

Purpose: To evaluate the feasibility of 3D intraoperative imaging with a freehand single photon emission computed tomography (SPECT) probe to guide tumor excision and sentinel node biopsy (SNB) in patients with impalpable breast cancer. Methods: The study was designed to evaluate 20 patients with impalpable breast cancer scheduled for radioguided occult lesion localization (ROLL) using an intratumoral radiocolloid deposit or radioactive iodine 125 seed (radioactive seed localization, RSL) with or without SNB. In case of ROLL, the radiocolloid (99mTc-nanocolloid) was intratumorally injected (40MBq) guided by ultrasound. When a SNB was also performed, a dose 120Mbq was injected, followed by lymphoscintigraphy at 15 minutes and 3 hours post injection for SN identification. In case of RSL, a 125I-seed (8.5MBq) was implanted in the tumor prior to neoadjuvant chemotherapy (2-4 months before operation) guided by ultrasound. Intraoperatively, a device combining a spatial localization system and two tracking targets fixed respectively on the gamma probe and on the patient was used. 3D images were generated and displayed in real time following a protocol based on freehand SPECT probe movements. Results: To date, 11 patients with an average age of 63 years (range 51-73) have been included (6 ROLL, 2 ROLL+SNB and 3 RSL). Freehand SPECT enabled visualization of the preoperatively marked lesions in all 11 patients. During surgery, freehand SPECT also provided distance estimations to the lesions, facilitating their retrieval. Freehand SPECT image acquisition took 131.5s for ROLL, 155.5s for ROLL+SLNB and 69.2s for RSL on average. Ex-vivo real time display of the radioactivity in the excised tissue specimen in relation to the margins of the specimen was performed in all patients. Histopathologic margins were tumor negative in all 11 cases, in accordance with the ex-vivo images. Conclusion: 3D intraoperative imaging using freehand SPECT may add valuable information to perform minimally invasive radioguided surgery in breast cancer. This technique may also be of value in other surgical applications involving tumor excision and SNB.

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The Reliability of the Identification of Lymphovascular Invasion in Breast Biopsy Specimens R.F. Van la Parra,[1]* A.H. Mulder,[2] J.H. De Wilt,[3] W.K. De Roos,[1] K. Bosscha.[4] *1. Surgery, Gelderse Vallei Hospital, Ede, Netherlands; 2. Rijnstate hospital, Arnhem, Netherlands; 3. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 4. Jeroen Bosch Hospital, 's Hertogenbosch, Netherlands.*

Background- Lymphovascular invasion (LVI) is a significant predictor for lymph node metastases in breast cancer and associated with a worse prognosis. Recently, LVI has been incorporated in a predictive model for sentinel node positivity. However, presence of lymphovascular invasion (LVI) is usually assessed at definitive pathology. The aim of this study was to determine if LVI can also be accurately identified in diagnostic breast biopsy specimens using not only conventional HE but also the endothelial markers CD31 and D2-40. Methods - We prospectively included 49 patients with an invasive breast cancer from November 2010 until March 2011. The diagnostic biopsy specimens were cut, measured and stained with HE, CD31 and D2-40. LVI was also determined on HE stained slides in all definitive specimens. Results- The diagnostic biopsy specimens varied in size between 0.6 and 4.8 cm. Lymphovascular invasion could not be identified in specimens smaller than 1,2 cm. Lymphovascular invasion was identified on 14/49 HE stained slides in the definitive specimens. Two of these cases were also identified on the HE stained biopsy slides, 4 on the CD31 stained biopsy slides and 4 on the D2-40 stained biopsy slides. The biopsy slides did not demonstrate LVI in 8/14 cases (false negative). In 5/49 cases the biopsy slides suggested LVI, which could not be confirmed on the definitive biopsy specimens (false positive). Conclusions- Lymphovascular invasion, assessed on definitive pathology specimens, could only be identified in a small percentage of biopsies taken from the same tumour specimens. Staining with the endothelial markers CD31 or D2-40 did not improve identification of LVI significantly. Therefore, based on these results, assessment of the presence of LVI in breast biopsy specimens is not considered suitable for routine use.

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The Relationship amongst Sentinel Lymph Node Metastasis Size, Extracapsular Extension and Outcomes in Breast Cancer K.J. Rosso,* D.S. Nathanson, D. Chitale, M. Mahan. *General Surgery, Henry Ford Health System, Detroit, MI.*

INTRODUCTION Metastasis to the sentinel lymph node (SLN) is associated with higher mortality than when SLNs are negative. We hypothesized that sentinel lymph node metastasis size (SLNMS) and extracapsular extension (ECE) would be predictive of systemic metastasis and death. METHODS Data from 1,963 women with breast cancer who underwent SLN dissection were prospectively collected and retrospectively analyzed. Cancer-specific mortality and all-cause mortality were calculated and multivariable analyses performed to identify significant interacting variables in terms of demographics, clinical stage, histology and pathological characteristics. SLNMS and ECE were evaluated pathologically. RESULTS Two hundred thirty (11.8%) treated patients died during the 16 year follow-up. The cause of death was known in 222 patients: 165 from non-cancer related or unknown causes and 57 from cancer. Median survival time of patients who died of cancer was 42 months (95% CI, 33-60). Patients under 40 years of age died of cancer at roughly twice the rate as patients in any other age group. SLNMS and ECE did not significantly affect mortality (p=0.340 and p=0.949, respectively). Age and stage significantly impacted (p<0.0001) all-cause mortality. Mortality increased by 5.5% with every one year increase in age. Progesterone receptor expression (p=0.0083) and stage (p=<0.0001) significantly impacted cancer-specific survival in multivariable analysis. SLNMS, lymphovascular invasion or ECE failed to gain statistical significance in either disease specific or all-cause mortality. CONCLUSIONS While stage and PR expression significantly affected disease specific mortality in our breast cancer patients, the size of sentinel lymph node metastasis and extracapsular extension did not.

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Three-dimensional Geometry of Breast Tumors: Implications for Lumpectomy Technique J.M. Buckley,* E.F. Brachtel, Y. Yagi, L.J. Fernandez, R. Tang, O.P. Aftreth, J.S. Michaelson, S.B. Coopey, M.C. Specht, M.A. Gadd, K.S. Hughes, F.C. Koerner, B.L. Smith. *Surgical Oncology, Massachusetts General Hospital, Boston, MA.*

Introduction: Lumpectomy with microscopically clear margins is a safe and effective approach for surgical management of breast cancer. Unfortunately, re-excision rates for positive lumpectomy margins are as high as 30-50%, as it is currently not possible to accurately determine the true shape and microscopic borders of a tumor preoperatively or intraoperatively. We sought to better understand the 3-D microanatomy of common breast cancer subtypes, and analyze their growth patterns within breast parenchyma. Methods: With IRB approval, prospective consent was obtained for the use of excess/discarded material from patients undergoing lumpectomy or mastectomy for breast cancer. Following standard clinical pathology processing, tissue blocks from 12 breast cancers were serially sectioned. H&E stained slides at 100μm intervals were scanned using Nanozoomer (Hamamatsu, Japan), a microscopic-resolution scanner. 3D reconstructions of tumors were created from scanned images using Reconstruct, open-access software. Results: Breast cancer subtypes have characteristic growth patterns within breast tissue which may have implications for lumpectomy surgery. A typical invasive ductal carcinoma has a spherical shape, with a spiculated surface representing tumor cells infiltrating into surrounding parenchyma. Ductal carcinoma in-situ (DCIS) appears to spread along long axis of the duct system, creating dilated, tortuous, tumor filled ducts. The classical invasive lobular carcinoma has a haphazard, linear, infiltrative growth pattern, and does not assume the definitive shape seen in the ductal carcinomas examined.(Figure 1) Conclusions: Invasive ductal and invasive lobular cancers appear to have very different growth patterns in three dimensions. DCIS appears to grow in a linear fashion along the duct network. The microanatomy studies described have the potential to guide refinements in lumpectomy technique.

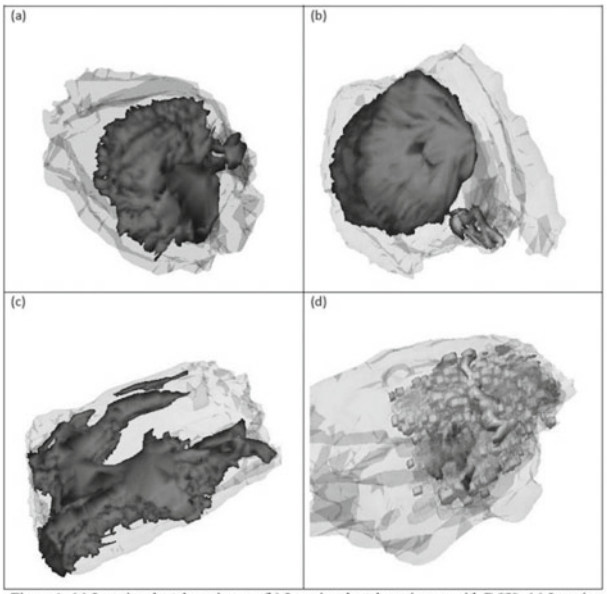

Figure 1: (a) Invasive ductal carcinoma, (b) Invasive ductal carcinoma with DCIS, (c) Invasive lobular carcinoma, (d) Mass-forming DCIS (dilated, tortuous duct represented in solid yellow). (Color code: Pink: Invasive carcinoma, Light blue: lumpectomy outline, Green: DCIS)

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Factors which Affect Use of Breast Conservation and Mastectomy in an Underinsured, County Hospital Population A.E. Klemens,[1] C. Hsu,[2] L. Olsen,[1] M.E. Bouton,[1] I.K. Komenaka.[1]* *1. Surgery, Maricopa Medical Center, Phoenix, AZ; 2. University of Arizona, Tucson, AZ.*

Background: Despite no difference in overall survival between lumpectomy and mastectomy, significant variation exists between institutions and within populations. Less data exists about minority populations. The current study was performed to evaluate variables that affect use of mastectomy and lumpectomy in a county hospital population. Methods: A retrospective review of all patients who underwent breast cancer operations from July 2001 to February 2011 at a county, safety net hospital. Sociodemographic, clinical, and treatment variables were evaluated. All patients with documented contraindications to breast conservation were excluded. Univariate analysis was performed to identify variables which were associated with type of operation. All

of the variables with a p-value <0.10 were included in the multivariate analysis. Results: The average age of the 412 patients included was 53 years. 81% of the patients were insured with Medicaid or uninsured and 37% were non-Hispanic White. Most patients (58%) presented with clinical stage 2A/B disease. Mastectomy was performed in 37% of patients and lumpectomy was accomplished in 63%. In unadjusted analysis, patients who were Hispanic or were uninsured were more likely to undergo lumpectomy. Patients with clinically palpable masses or lymph nodes, as well as increased clinical tumor size, pathologic tumor size, lymph node involvement, higher pathologic stage and increased histologic grade were associated with increased likelihood of mastectomy. Use of preoperative chemotherapy and type of surgeon was associated with increased likelihood of lumpectomy. In adjusted analysis, clinical tumor size (p = 0.035) and pathologic stage (p = 0.003) remained associated with mastectomy, while use of preoperative chemotherapy (p = 0.004) and type of surgeon (p = 0.001) was associated with lumpectomy. Conclusions: In this underinsured, county hospital population, larger clinical tumor size and higher pathologic stage are associated with increased likelihood of mastectomy. Use of preoperative chemotherapy was associated with increased likelihood of lumpectomy. Type of surgeon can also affect patient choice of breast operation.

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Factors Which Affect Use of Breast Conservation and Mastectomy in Hispanic Patients from a County Hospital Population A.E. Klemens,[1] L. Olsen,[1] C. Hsu,[2] M.E. Bouton,[1] J. Nodora,[2] M. Martinez,[2] P.A. Thompson,[2] I.K. Komenaka.[1]* *1. Surgery, Maricopa Medical Center, Phoenix, AZ; 2. University of Arizona, Tucson, AZ.*

Background: Despite no difference in overall survival between lumpectomy and mastectomy, significant variation exists throughout the country. Much less data exists about cancer treatment in Hispanics. The current study was performed to evaluate variables that affect use of mastectomy and lumpectomy in a Hispanic population. Methods: A retrospective review of all Hispanic patients who underwent breast cancer operations from July 2001 to February 2011 at a county, safety net hospital. Sociodemographic, clinical, and treatment variables were evaluated. All patients with documented contraindications to breast conservation were excluded. Univariate analysis was performed to identify variables which were associated with type of operation. All of the variables with a p-value <0.10 were included in the multivariate analysis. Results: The average age of the 219 patients included was 49 years. 93% of the patients were insured with Medicaid (23%) or uninsured (70%). Only 24% of patients underwent screening mammography and most patients (59%) presented with clinical stage 2A/B disease. Mastectomy was performed in 33% of patients and lumpectomy was accomplished in 67%. In unadjusted analysis, patients who presented with clinically palpable masses or lymph nodes, as well as increased pathologic tumor size, lymph node status, and stage, increased histologic grade, and Her2neu positivity were associated with increased likelihood of mastectomy. Higher BMI, hormone receptor positivity, and type of surgeon were associated with increased likelihood of lumpectomy. In adjusted analysis, pathologic stage (p = 0.01) remained associated with mastectomy, while primary language (Spanish, p = 0.04), higher BMI (p = 0.04), use of preoperative chemotherapy (p = 0.01) and type of surgeon (p = 0.002) were associated with lumpectomy. Conclusions: In this underinsured, Hispanic population, higher pathologic stage was associated with increased likelihood of mastectomy. Higher BMI and use of preoperative chemotherapy were associated with increased likelihood of lumpectomy. Type of surgeon and primary language of the patient may also affect patient choice of breast operation.

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Intraoperative Sentinel Lymph Node Evaluation is Accurate after Neoadjuvant Therapy for Breast Cancer C. Akay,[1]* T. Whitsell,[2] C. Albarracin,[1] K.K. Hunt,[1] R. Bassett,[1] E.A. Mittendorf,[1] M. Yi,[1] A. Sahin,[1] S. Krishnamurthy,[1] H. Kuerer,[1] F. Meric-Bernstam,[1] G.V. Babiera,[1] I. Bedrosian,[1] R.F. Hwang.[1] *1. The University of Texas MD Anderson Cancer Center, Houston, TX; 2. Mercy Medical Center, Des Moines, IA.*

Objective: The accuracy of intraoperative sentinel lymph node (SLN) evaluation to detect metastasis after neoadjuvant therapy has been questioned. Our objective was to identify clinicopathologic factors impacting the accuracy of intraoperative SLN evaluation. Methods: We reviewed the records of 1579 breast cancer patients who underwent SLN biopsy and intraoperative pathologic evaluation by touch prep and/or frozen section from 2004-2007. Intraoperative results were compared to analysis of permanent sections. SLNs that were positive on final analysis but initially reported as negative were recorded as false negative (FN) events. Tumor size, histology, grade, receptor status, lymphovascular invasion (LVI), multifocality, type of surgery, SLN metastasis size, receipt of neoadjuvant therapy, number of SLNs and nonsentinel nodes harvested and intraoperative assessment method were evaluated. Univariate and multivariate analyses were used to identify factors associated with a FN event. Results: Most tumors were invasive ductal (IDC, 71%), invasive lobular (ILC, 9%) or mixed IDC/ILC (8%). LVI was present in 292 (20%) and most were grade 2 (47%) or 3 (39%). Neoadjuvant endocrine or chemotherapy was utilized in 483 (31%) patients. There were 378 (24%) patients with a positive SLN on final pathology; of these, 189 (50%) had a FN intraoperative evaluation. There was no significant difference in FN rate between those patients who received neoadjuvant treatment versus those who did not (49% vs 54%, p=0.4). Univariate analysis revealed that ILC histology, ER or PR positivity and touch prep were associated with a higher FN rate whereas grade 3, HER2 positivity, and LVI were associated with a lower FN rate. On multivariate analysis (table), touch prep evaluation was associated with a higher FN rate (OR 4.17, p<.0001) and high grade was associated with a lower FN rate (OR=0.46, p=0.01). Conclusion: Accuracy of intraoperative SLN evaluation for breast cancer is greater in high grade tumors and is not affected by neoadjuvant therapy. Intraoperative SLN assessment is a reliable technique for guiding axillary treatment decisions in patients who receive neoadjuvant treatment.

Variable		Odds Ratio	95% CI	P-value
Grade	1	---	---	0.01
	2	1.11	0.51, 2.42	
	3	0.46	0.19, 1.12	
LVI	No	---	---	0.06
	Yes	0.61	0.37, 1.03	
Method of Intraoperative Evaluation	FS	---	---	<.0001
	TP	4.17	2.33, 7.48	
	FS + TP	0.58	0.28, 1.21	

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Is Radiation Indicated in Patients with T1-T2 Breast Cancer with Close or Positive Margins after Mastectomy? S. Dougherty, J. Urbanic, J. Stewart, E. Levine, M. Howard-McNatt.* *Wake Forest School of Medicine, Winston-Salem, NC.*

In clinical practice patients with a positive surgical margin are often treated with post mastectomy radiation therapy (PMRT). However, there is little data supporting this practice. This study examined recurrence and survival among women with T1 and T2 disease with 0-3 positive lymph nodes for metastatic disease who had a close or positive margin after mastectomy. METHODS: The pathology reports of 378 patients treated with a mastectomy between 1999-2009 at our institution were reviewed. Of these 48 patients had a positive or < 2mm margin. Patients with more established indications for PMRT including T3-4 disease or > 4 lymph nodes were excluded. Demographic, tumor, treatment regimens, and Kaplan-Meier relapse free and overall survival were compared between women who were treated with (n=18) and without (n=35) PMRT. RESULTS: Median follow-up was 4.5 months. There was no difference between age, tumor size, grade, lymphovascular invasion, estrogen receptor status and number of metastatic lymph nodes between the groups. Patients who were treated with PMRT tended to receive chemotherapy in comparison to the no PMRT group (p=0.02).Three patients had local recurrences, three distant recurrences, and there were three deaths. All of the recurrences occurred in the non PMRT group. The risk of localregional failure in this series was 8.5% in patients who did not receive PMRT and 0% in patients who received PMRT. There was no correlation with locoregional failure as to age, ER status, LVI or grade. All patients that failed had T1or T2 cancers. The Kaplan-Meier mean survival was 49 months and recurrence free survival was 32 months in the no PMRT group. CONCLUSION: A close or positive margin is uncommon after mastectomy in patients with < 5 cm

tumor and 0-3 positive axillary nodes. PMRT decreased the risk of patients with T1-2 tumors from having a localregional recurrence and should be considered in this population.

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State and Federal Health Policy and Its Effects on Racial Disparities in Breast Cancer Reconstruction R.L. Yang,* I.C. Lin, A.S. Newman, C.E. Reinke, G.C. Karakousis, B.J. Czerniecki, L.C. Wu, R.R. Kelz. *University of Pennsylvania School of Medicine, Philadelphia, PA.*

Background: In order to improve access to reconstruction for post-mastectomy patients, Pennsylvania adopted the Breast Cancer Reconstruction Surgery Coverage Act in 1997. Additionally, federal policies were passed in the years of 1998-2000 further mandating insurance coverage of all post-mastectomy breast reconstruction (PMBR). This study was designed to identify disparities in diffusion of policy into practice for frequently underserved groups. Methods: Patients greater than 18 years old who had mastectomy were identified in the Pennsylvania Health Care Cost Containment Council inpatient database from 1994 to 2004. International Classification of Disease-9 procedure codes were used to identify patients who underwent immediate PMBR. Rates of PMBR prior to (1994-1997) and following (2001-2004) the federal and state policy changes were examined by race, age, median income, and Elixhauser comorbidity index using a chi-square test. Multivariable logistic regression analysis was performed to evaluate the relationship between race and PMBR before and after the policy changes with adjustment for confounders. Results: We identified 35,206 patients who underwent a mastectomy during the study time interval, with 18.49% undergoing PMBR prior to policy changes and 27.58% following policy changes. Prior to policy changes, the adjusted model showed that both black patients and Asian patients were less likely to undergo PMBR (OR 0.76, CI 0.61-0.94; OR 0.20, 95% CI 0.09-0.54) when compared to white patients. Following the policy changes, the adjusted model showed that when compared to white patients, black patients no longer had a statistically significant difference in reconstruction (OR 0.88, 95% CI 0.74-1.04), although Asian patients still were slightly less likely to undergo reconstruction (OR 0.39, 95% CI 0.24-0.63). Conclusions: Changes in National and Pennsylvania policy were associated with a reduction in PMBR racial disparities. The improvements seen were not equal across all racial groups. Future studies are needed to investigate the role of cultural preferences in utilization of PMBR that might explain the residual disparities.

Racial Trends in the Likelihood of Women in Pennsylvania Undergoing Breast Reconstruction, Before and After State and Federal Policy Changes

	White (n = 8,991)	Black (n =1,165)	Asian (n = 51)	Other* (n = 114)	Unknown (n = 825)	P Value**
Pre-policy time period, 1994-1997						
Percent of patients who underwent PMBR	18.46%	15.45%	11.76%	14.91%	24.00%	(<0.001)
Adjusted OR (95% CI)***	1.0	0.76 (0.61-0.94)	0.22 (0.09-0.54)	0.44 (0.24-0.79)	1.46 (1.20-1.78)	---
P Value	---	0.012	0.001	0.006	<0.001	---
Post-policy time period, 2001-2004						
	White (n = 13,175)	Black (n =1,295)	Asian (n = 110)	Other* (n = 143)	Unknown (n = 898)	P Value**
Percent of patients who underwent PMBR	27.55%	24.56%	25.45%	23.08%	33.30%	(<0.001)
Adjusted OR (95% CI)***	1.0	0.88 (0.74-1.04)	0.39 (0.24-0.63)	0.51 (0.83-1.16)	1.10 (0.92-1.32)	---
P Value	----	0.122	<0.001	0.003	0.282	---

*Hispanics, American Indians, Alaskan Natives and patients of more than one race were combined into the "other" category due to small sample sizes.
**Pearson Chi Square was calculated to determine differences in reconstruction rates based on race. P-values <0.05 are significant.
***Adjusted OR were determined by logistic regression of race as a predictor of breast reconstruction for the pre-policy and post-policy time periods with adjustment for age, median income, and Elixhauser comorbidity index. P values <0.05 are significant.

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Assessment of Pathologic Tumor Response to Neoadjuvant Endocrine Therapy in Postmenopausal Women with Estrogen Receptor Positive Stage 2 or 3 Breast Cancer Y.R. Tammaro,* G. Moses, A. Eastman, Y. Peng, D. Euhus, A. Leitch. *University of Texas Southwestern Medical Center, Dallas, TX.*

Purpose Assessment of Residual Cancer Burden (RCB) has been proposed by MD Anderson Cancer Center as a prognostic tool for breast cancer patients treated with neoadjuvant chemotherapy. Previous studies demonstrated that neoadjuvant therapy reduced tumor proliferative index (Ki67 expression). In this study; we examined both RCB and Ki67 expression in postmenopausal women with estrogen receptor (ER) positive stage 2 or 3 breast cancer to evaluate pathologic tumor response to neoadjuvant endocrine (aromatase inhibitor) therapy. Patients and Methods From a single institution database, we identified 18 stage 2 or 3 breast cancer patients receiving neoadjuvant aromatase inhibitor therapy for 16-18 weeks prior to surgery between 2006 and 2009. Clinical response, pathologic response (RCB) and modulation of proliferation (Ki 67 expression) were assessed. Results Average clinical tumor size prior to and after neoadjuvant therapy was 4.67 and 2.70 cm, respectively. 57.9% exhibited a partial clinical response, 31.6% stable disease, and 10.5% complete clinical response. There were no pathological complete responses. RCB was class II for 47.4% of tumors and class III for 52.6% of tumors. Proliferation was reduced a mean of 82.2% in 15 of 17 evaluable tumors (P=0.0004). Conclusion A short course of neoadjuvant aromatase inhibitor therapy in postmenopausal women with ER positive stage 2 or 3 breast cancer significantly reduced proliferation and was associated with significant reductions in clinical tumor size. Nearly half of the patients had an intermediate RCB of II, although there were no complete pathologic responses. The MD Anderson study revealed that in patients treated with neoadjuvant chemotherapy, RCB of II was associated with a better prognosis than RCB III. A combination of pathologic assessment of RCB and Ki67 may identify a favorable prognostic cohort among patients treated with neoadjuvant endocrine therapy who may avoid additional adjuvant chemotherapy despite having residual disease.

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Delays in Time to Treatment for Triple Negative Breast Cancer A. Eastman,* R. Rao, D. Euhus, M. Leitch, V. Andrews, A. Moldrem, J. Huth, Y. Tammaro. *University of Texas Southwestern, Dallas, TX.*

BACKGROUND: The acceptable time interval from a diagnosis of breast cancer to initiation of treatment is an area of controversy. While it is agreed upon that therapy should be started as promptly as possible, the current multidisciplinary approach to breast cancer treatment can sometimes require additional work-up, including imaging and consultations, which may delay treatment. In general, delays of less than 90 days have not been found to negatively impact oncologic outcome. It remains unknown, however, whether aggressive breast cancer subtypes, specifically triple negative tumors, are more time sensitive. The purpose of this study was to evaluate whether delays from diagnosis to initial treatment in patients with triple negative breast cancer impacts survival. METHODS: A retrospective review of patients with triple negative breast cancer undergoing treatment between January 2004 and January 2011 in a comprehensive, multidisciplinary breast oncology program was undertaken. Data regarding demographics, stage, pathology, treatment and survival were obtained. Interval to treatment was calculated as the number of days from the date of pathologic diagnosis to first treatment, whether local or systemic. Prolonged interval to treatment was defined as greater than 45 days. Overall survival was compared between patients with short versus prolonged delays. RESULTS: 207 patients with triple negative breast cancer were included in our study population. Mean+SEM interval to treatment was 37+2 days. The majority of patients were African-American (46%, n=96). There were 46 deaths (22%). As expected, higher stage at presentation yielded worse overall survival (fig 1a), p<0.0001. Interval to treatment, however, had no significant effect overall survival (fig 1b), p=0.97. CONCLUSIONS: For patients with triple negative breast cancer, a short delay from pathologic diagnosis to initial treatment does not appear to adversely affect survival. Appropriate time to perform necessary evaluations (genetic testing, imaging, consultation) can be obtained to guide optimal treatment options.

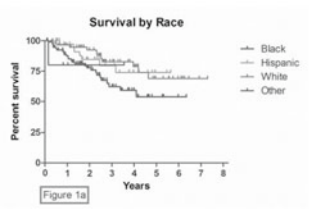

Figure 1a

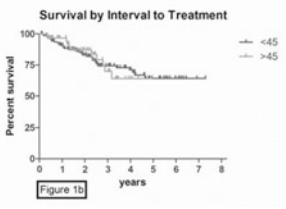

Figure 1b

P139

Withaferin A Down-regulates Breast Cancer Susceptibility Gene-1, Heat Shock Factor-1, Mutant p53, and Induces Apoptosis in Triple Negative Breast Cancer Cells X. Zhang, A.K. Samadi, R. Mukerji, M.S. Cohen.* *Department of Surgery, University of Kansas Medical Center, Kansas City, KS.*

Background: Triple negative breast cancers remain a challenge for treatment with cytotoxic therapies lacking durable efficacy resulting in the need for novel and improved therapeutics. The purpose of this study was to examine the efficacy of a natural withanolide Withaferin A(WA) in triple negative breast cancer cell lines in vitro, and identify its novel molecular therapeutic targets in this disease. Methods: The effects of Withaferin A on cell viability were examined in various triple negative breast cancer cell lines using MTS assay. The mechanisms of action were further analyzed in MDA-MB-231 cells using annexin V/propidium iodide flow cytometry(FC) and confirmed using Western Blot analysis. Results: Withaferin A treatment(72hrs) significantly decreased cell viability in four triple negative breast cancer cell lines with IC50 concentrations of 542 nM for MDA-MB-231 cells, 425 nM for MDA-MB-468 cells, 432 nM for HCC1937 cells, and 246 nM for BT20 cells. The drug is very selective for these breast cancer cells with MRC-5 fetal lung fibroblast control cells having a relative resistance to WA(IC50=6.42μM). WA also induced apoptosis in MDA-MB-231 at 2.5μM treatment for 24 hours by FC. Western analysis confirmed that this apoptotic effect was accompanied by increased poly(ADP-ribose) polymerase (PARP) cleavage and caspase-3 activation at 2X IC50 concentrations. Further analysis of molecular changes indicated a marked decrease in both total Akt and phospho-Akt(ser473) protein levels after 24 h treatment with 2.5 μM WA. In addition, WA significantly decreased the protein expression levels of breast cancer susceptibility gene-1(BRCA-1), heat shock factor 1 (HSF-1), and mutant p53 in a dose-dependent manner, with marked reduction in all these three proteins at 24 h after 2.5 μM WA treatment. Conclusions: WA inhibits the viability of multiple triple negative breast cancer cells. The anti-cancer effects of WA in triple negative MDA-MB-231 breast cancer cells are associated with down-regulation of BRCA-1, HSF-1, and mutant-p53 proteins and induction of apoptosis in part through the PI3K/Akt pathway.

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HER 2 Neu Positive Status of the Primary Tumor Predicts Axillary Lymph Node Response in ER/PR +, Node Positive Patients Receiving Neoadjuvant Chemotherapy L. Sparber, V. Murthy, E. Carey, S. Schaefer, E.J. Santoro, J. McDermott, R.S. Chamberlain, M.M. Blackwood.* *Surgery - Breast Health & Disease Management, St. Barnabas Medical Center, Livingston, NJ.*

Introduction: Neoadjuvant chemotherapy (NAC) is commonly used in patients with operable/advanced breast cancer who wish to pursue breast conservation. NAC can generate an in vivo response in both the primary tumor and the axillary lymph nodes. The use of NAC has led to increased interest in minimally invasive approaches to axillary staging such as sentinel lymph node biopsy (SLNB), and avoidance of axillary dissection. This pilot study sought to evaluate whether ER/PR and HER 2 neu status of the primary tumor could predict sentinel lymph node positivity in clinically N+ patients undergoing NAC. Methods: 41 patients underwent SLNB following NAC (Anthracycline/Taxane/Herceptin based) between July 2009 and August 2011. 86% of patients (N = 37) had a SLNB followed by axillary lymph node dissection (Levels I/II). SLNs were evaluated with cytokeratin immunohistochemical stain (AE1-AE3). Data regarding the SLNs in the affected axilla and the ER/PR and HER 2 neu status of the primary tumor was collected and univariate analysis was performed to determine factors predictive of SLN positivity. Results: 41 patients underwent SLNB following NAC, with a median age of 50 years. Stage IIB or Stage IIIA invasive ductal carcinoma was the most common indication for NAC. 8 patients had complete primary and axillary response to NAC (19.5%). 90% of ER+/PR+ and HER 2 neu + patients (n = 9/10) had a negative SLNB following NAC (Luminal B), compared patients who were ER+/PR+ but HER 2 neu negative, who had a negative SLNB only 45.8% (N = 11/24) of the time (Luminal A). T stage, clinical stage, and histology (ductal versus lobular) were not significant factors in SLN response to NAC. Conclusion: SLNB is feasible in patients with locally advanced/operable breast cancer following NAC. Luminal B patients have a higher axillary response rate following NAC than do luminal A patients. This fact may serve as a useful predictive model which can be used to identify patients at greater risk of local/regional failure after NAC. Further validation of these results is warranted.

Comparison of SLNB positive and negative patient groups after receiving neoadjuvant chemotherapy

Patient characteristics:	SLNB positive following NAC (N=18)	SLNB negative following NAC (N=23)	P value
Median age	48	51	
Tumor characteristics on affected side:			
Histology			
Invasive ductal carcinoma	14 (40%)	21 (60%)	
Invasive lobular carcinoma	4 (66.6%)	2 (33.3%)	
Stage prior to NAC			
2A	2 (40%)	3 (60%)	
2B	7 (46.6%)	8 (53.3%)	
3A	7 (46.6%)	8 (53.3%)	
3B	1 (25%)	3 (75%)	
3C	1 (50%)	1 (50%)	
T stage after final histopathology			
ypT0	0 (0%)	8 (100%)	
ypT1	8 (47%)	9 (52.9%)	
ypT2	7 (70%)	3 (30%)	
ypT3	3 (75%)	1 (25%)	
ypTx	0 (0%)	2 (100%)	
Receptor and HER2 status			0.1
ER+ PR+ HER2- (Luminal A)	13 (54.1%)	11 (45.8%)	
ER+ PR+ HER2+ (Luminal B)	1 (10%)	9 (90%)	
ER- PR- HER2- (Triple negative)	3 (60%)	2 (40%)	
ER- PR- HER2+ (HER2 overexpression)	1 (50%)	1 (50%)	

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Intraoperative Assessment of Sentinel Nodes Using Rapid Digital Imaging: A Pilot Study C.S. Kaufman,[1]* L. Hill,[2] R. Caro,[3] S. Nix,[3] J. Szenasi,[3] K. Ness,[3] N. Schnell,[3] C. Mahon,[3] L. Gambrell.[3] *1. Bellingham Breast Center, University of Washington, Bellingham, WA; 2. Bellingham Regional Breast Center, Bellingham, WA; 3. Bellingham Surgery Center, Bellingham, WA.*

Sentinel node biopsy is the standard of care for clinically node negative stage 1 & 2 invasive breast cancer. Use of touch preps or frozen section intraoperatively has problems with accuracy as well as the time it takes to obtain results. We investigated the use of intraoperative digital nodal xray to provide predictive evidence of the presence of lymph node metastases in sentinel node biopsy. Methods: Consecutive breast cancer patients who required sentinel node biopsy (SNB) were evaluated by intraoperative digital xray as well as intraoperative touch prep or frozen section. Each specimen and digital image (available within a minute of excision) was assessed intraoperatively by surgeon and radiologist followed by the pathologist using touch prep/frozen as well as permanent sections. Surgeon and radiologist graded each patient's images whether there were metastases or not. They were blinded to each other's opinions as well as any pathology data. Surgeon and radiologist impressions were compared to pathologists' intraoperative assessment as well as the final H&E report. Results: There were 39 consecutive breast cancer patients who underwent SNB between February and September 2011. Of these, final H&E results found 26 negative node patients and 13 positive node patients. Of the positive nodes, 9 were macrometastases and 4 were micrometastases. Intraoperative pathologist evaluation with touch prep found 7 of 9 macrometastases but only 1 of 4 micrometastases. In addition, all 26 negative nodes were predicted. Surgeons similarly predicted 7 macrometastases but none of the micromets. Surgeons identified 24/26 negative SNB. Radiologists predicted 6/7 macrometastases and 1/7 micromets. Radiologists identified only 18/26 negative SNB correctly. Surgeons' performance using digital imaging of SNB was equally

accurate as the pathologist performing touch prep/frozen sections in predicting positive nodes and 92% as accurate in predicting negative nodes. Conclusion: A pilot study of intraoperative assessment of SNB using rapid digital xray supports a new method ofpredicting the presence of positive sentinel nodes. Further study is suggested for this rapid inexpensive method.

Sentinel Node Biopsy Predictions Using Rapid Imaging

	Surgeons	Radiologists	Intraopeartive touch prep/frozen	Final H&E Pathology of nodes
Macrometastases	7	6	7	9
Micrometastases	0	1	1	4
Negative Sentinel nodes	24	15	26	26

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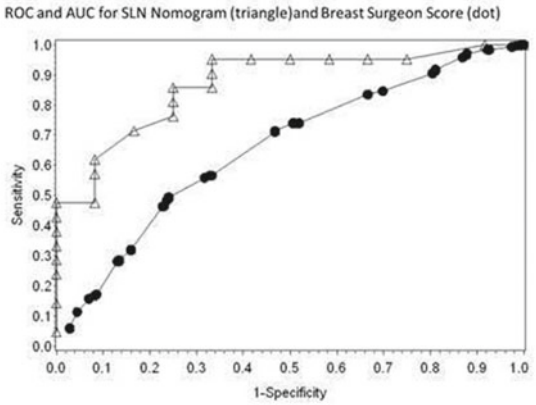
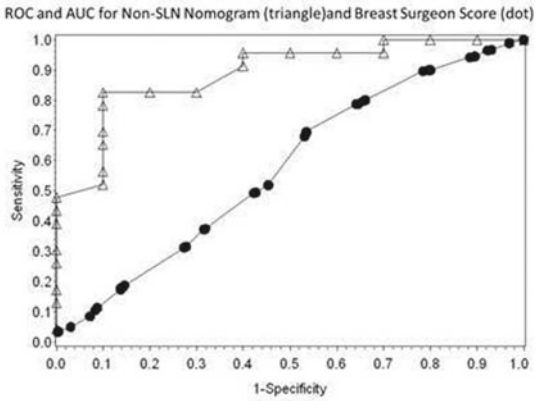
Predicting Sentinel and Non-sentinel Node Metastases: A Comparison of Breast Surgeons and Nomograms P.R. De Alcantara Filho,[1]* L. Sugaya,[1] B.S. Mota,[1] S. Patil,[2] K.J. Van Zee,[2] J.B. Bevilacqua.[1]
1. Hospital Sirio-Libanes, Sao Paulo, SP, Brazil; 2. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: Memorial Sloan-Kettering Cancer Center (MSKCC) developed nomograms to predict the likelihood of sentinel lymph node (SLN) metastases in patients with invasive breast cancer (SLNN) and to predict the likelihood of residual axillary disease after a positive SLN biopsy (NSLNN). We sought to compare the accuracy of the nomograms and breast surgeon predictions. We also investigated whether the nomogram results would influence the surgeon clinical decisions. Methods: Two sets of 33 patients were randomly selected from the MSKCC Sentinel Node database. The first included only patients with invasive breast cancer and the second included only patients with invasive breast cancer and positive SLN biopsy. 26 randomly selected surgeons from the Brazilian Society of Breast Surgeons were asked to estimate the probability of each patient having SLN metastases or non-SLN metastases in case of positive SLN biopsy. The surgeons were also asked whether the nomogram results would change their clinical management. The predictions of the nomograms and breast surgeons were compared, and changes in surgical decisions were analyzed. Results: There was no correlation between nomogram predictions and breast surgeon estimates for either the SLNN or the NSLNN. The area under the receiver operating characteristics curves (AUCs) were 0.871 and 0.657 for SLNN and breast surgeons, respectively ($p<0.0001$). The AUCs were 0.889 and 0.575 for NSLNN and breast surgeons, respectively ($p<0.0001$). McNemar's test found no significant changes in breast surgeons' decisions after receiving either nomogram's results. Conclusions: The nomograms were significantly more accurate than the breast surgeons in predicting SLN metastases and in predicting residual axillary disease after a positive sentinel node. Perhaps due to their unfamiliarity with the nomograms and their accuracy, Brazilian breast surgeons were unlikely to change their decisions based on the predictions of the nomograms.





P143

Factors Affecting Recruitment to a Pre-surgical Window Trial of 4-hydroxytamoxifen for Ductal Carcinoma In Situ L.R. Spiguel,* K. Page, J. Shklovskaya, C. Gresik, K. Bethke, N. Hansen, S. Khan.
Lynn Sage Breast Center, Northwestern University, Chicago, IL.

Introduction: Pre-surgical window trials for ductal carcinoma in situ (DCIS) are important for the testing of new prevention agents, but have not been widely used. We describe the recruitment experience in an on-going study testing transdermal 4-hydroxytamoxifen (4-OHT), a potent tamoxifen metabolite, against oral tamoxifen, with the endpoint of cell proliferation pre and post therapy. Our hypothesis is that transdermal 4-OHT would decrease toxicity while maintaining efficacy. Methods: We reviewed prospectively collected data on all eligible DCIS patients between November 2009 and August 2011. Of these, the fraction interested in the study and reasons for study refusal were examined, comparing initial eligibility criteria to after modification of criteria in 11/2010. Initial criteria included all adult patients with a diagnosis of non-palpable ER positive, grade 2-3 DCIS, non-comedo, no evidence of microinvasion, and no mass lesion ≥ 5mm or area of calcifications > 5 cm. Modified criteria included all grades of DCIS, and exclusions related to radiologic size and microinvasion were removed. The compensation for time and travel was also increased. All patients were to apply topical 4-OHT for 6 weeks prior to surgical excision. Results: Of the 316 patients, 130 (41%) patients were eligible. Prior to the revised eligibility criteria, 43 (22%) patients were eligible, which increased to 70% following modification. Only 14% of patients were willing to consider participation, and this did not change with the modified inclusion criteria. The leading cause for refusal was delay in treatment as demonstrated in table 1. Of the patients who were uninterested, only 27% of patients went on to use tamoxifen as an adjuvant therapy, 10% refused, medically not recommended in 17%, and 45% undocumented due to surgery at another institution or tamoxifen decision pending. Conclusion: These data demonstrate the importance of broad inclusion criteria for successful accrual, by increasing the eligible population, and in turn should be a crucial consideration for study design. The largest barrier to participation was the delay in surgical therapy.

Table 1

	Initial Criteria (n)	Modified Criteria (n)	Total (n)
DCIS Patients	192	124	316
Eligible	(43)22%	(87)70%	(130)41%
Interest in Study	(6)14%	(13)14%	(18)14%
Refusal Reasons:			
Extra Visits	(5)12%	(3)3%	(9)7%
Surgery Elsewhere	(6)14%	(3)3%	(9)7%
Tamoxifen Use	(6)14%	(16)18%	(22)17%
Surgical Delay	(20)47%	(44)51%	(64)49%

P144

Effects of Public Policy on Insurance Specific Breast Cancer Outcomes W.C. Dooley,* J. Bong, J. Parker. *Breast Institute, University of Oklahoma, Oklahoma City, OK.*

Introduction: Our state made several changes in public policy related to breast cancer care. This study was designed to define the effects of those policy changes on outcomes for breast cancer care. Methods: This is an IRB approved, retrospective review of all breast cancer patients receiving primary treatment at a single institution from 1/1/1995 to 12/31/2008. Details of pathology, surgical therapy, chemotherapy, hormonal therapy and radiation therapy and survival were compared insurance classes of HMO, traditional insurance, Medicare, Medicaid, and no insurance/self pay. Results: During the time period, there were 2192 patients who received primary breast cancer treatment at this institution. The mean age was 57 and mean follow-up >60 months. Stage distribution was similar between HMO, traditional insurance and Medicare but lower rates of early stage disease for no insurance and Medicaid. We divided the data into 3 time periods. From 1995 to 1999 was a period of formal breast center function but no additional governmental policy changes. From 2000 to 2003 was a period of joint state and private funding of disease specific endowed chairs . In 2004 the state enacted a tobacco tax which funded a disease specific Medicaid for women at or below 186% of the Federal poverty level which covered all medical care. Table 1 shows the trends in overall survival. Medicaid patients had improved outcomes ($p<0.02$) in the final time period (2004-2008). As an overall group, stage specific outcomes improved across all insurance categories in the transition between 1995-1999 and 2000-2003. The new changes to Medicaid in 2004 had a dramatic effect on overall survival and non-breast cancer specific deaths. Decreased disparities between racial and ethnic groups in survival outcomes paralleled the improvements seen with the new Medicaid program. Conclusions : Funding of state medical schools to support academic activity in breast cancer can lead to improved outcomes in the university academic setting. Funding full Medicaid coverage for all health care in under-insured and un-insured low income patients decreases deaths from all causes and narrows disparities related to income but also race and ethnicity.

Overall Five Year Survival

Insurance type	1995-1999	2000-2003	2004-2008
HMO	81%	90%	91%
Traditional Insurance	78%	87%	82%
No Insurance	73%	76%	77%
Medicare	70%	72%	76%
Medicaid	63%	67%	77%

P145

Bilateral Analysis of the Vascular Surface of the Internal Mammary Arteries and Veins in Patients with and without Breast Cancer on Breast MRI R. Schipper,[1]* R. Dikmans,[3] M. Lobbes,[2] M. Smidt,[1] C. Boetes.[2] *1. Maastricht University Medical Center (MUMC) - Department of Surgery, Maastricht, Netherlands; 2. Maastricht University Medical Center (MUMC) - Department of Radiology, Maastricht, Netherlands; 3. Maastricht University Medical Center (MUMC) - Department of Plastic Surgery, Maastricht, Netherlands.*

Background - Magnetic Resonance Imaging (MRI) has become an important modality in the diagnostic work-up of breast cancer patients. MRI is the most accurate method for detecting breast cancer, but only with 72% specificity. Several studies have demonstrated a positive correlation between presence of breast cancer and increased breast vascularity, but these studies were not able to improve the specificity of the MRI. The aim of this study is to analyze the bilateral differences in the vascular surface of the internal mammary artery (IMA) and vein (IMV) in patients with established breast cancer versus healthy control patients. Methods – Breast MRI of 135 patients were analyzed. Measurements were performed on a 3D, T2 turbo spin echo sequence. Imaging parameters: Slice thickness 1 mm, field-of-view 280x338, reconstructed matrix 352, resulting in a in-plane resolution of 0.97x0.97 mm. Surface of both the IMA and IMV has been determined on both sides on the second and third intercostal space (ICS) by two independent readers. Results - Analysis of the surface measurements performed by reader 1 of the IMA & IMV in patients without breast cancer showed no significant differences between both sides with a mean surface of the IMA in the 2nd ICS left of 4.22 mm2 (range 1.99-12.41) and right 4.22 (2.08-11.06). The adjusted difference was 0.02 mm2 ($p=0.842$). The measurements by reader 2 confirmed all results of reader 1. In patients with unilateral breast cancer, reader 1 reported a significant difference in the vascular surface of the IMA & IMV in 2nd as well as in the 3rd ICS between the healthy and malignant side. For the IMA in the 2nd ICS the largest adaptation is reported with a mean adjusted difference for reader 1 of 1.26 mm2 ($p<0.001$). The results of reader 2 showed similar results as reader 1. Conclusion – The vascular surfaces of IMA and IMV were significant different on the side with breast cancer compared to the contra lateral side. This difference was not observed in healthy controls. Future research should proof whether the vascular surface could be a supplementary parameter in the assessment of breast MRI.

P146

Immediate Breast Reconstruction after Skin-sparing Mastectomy Does Not Increase the Risk of Locoregional Recurrence or Distant Metastases D. Van Mierlo,* O. Van Waardhuizen, R. Schipper, M. Martens, K. Keymeulen, W. Peeters, M. Lobbes, C. Boetes, E. Heuts, M. Smidt. *Maastricht University Medical Centre, Maastricht, Netherlands.*

Background: Immediate breast reconstruction (IBR) after skin-sparing mastectomy (SSM) offers breast cancer patients enormous advantages in terms of QOL and number of operations. A disadvantage of SSM with IBR is the inevitable retaining breast tissue in the skin flap. The clinical consequence is local recurrence (LR) and a possibly higher rate of distant metastases. Most studies concerning this issue show low patient numbers and/or a short follow-up. An accepted recurrence rate for mastectomy is 0.5-1% per year. The aim of this study was to evaluate the incidence of recurrence after SSM with IBR in patients operated on for invasive breast cancer (IBC), ductal carcinoma in situ (DCIS) or prophylactic indication in a single dedicated institute. Methods: Data of all SSM's with IBR patients were both retro- and prospectively collected in a database. 181 patients underwent a total of 244 SSM's with IBR for the following indications: IBC (n= 109), DCIS (n= 48) or prophylactic risk reduction (n= 87) between 2004 and 2011. Data concerning diagnosis, the pathology report, the (neo-) adjuvant therapy and follow-up were collected. Patient and tumour characteristics concerning DCIS and IBC were collected in Table 1. Results: All SSM and IBR were performed by dedicated oncologic and plastic surgeons. A total of 244 reconstruction procedures were performed. The tissue expander and deep inferior epigastric perforators were the most common procedures. The median follow-up was 26.5 (range 1-87) months. Local recurrence (LR) occurred in 4 patients (2.2 %) and was detected after a period of 16, 19, 21 and 25 months, respectively. All of these patients were initially treated for IBC. Only one patient also developed synchronic distant metastases. The median age of the patients with a prophylactic SSM + IBR was 52 years (range 26-71). In four patients malignant tissue was detected in definitive histopathology. None of the patients had a recurrence or a primary breast tumour in follow-up. Conclusions: SSM with IBR carries no increased risk for locoregional or distant recurrence compared to a non-skin sparing mastectomy in our single institute.

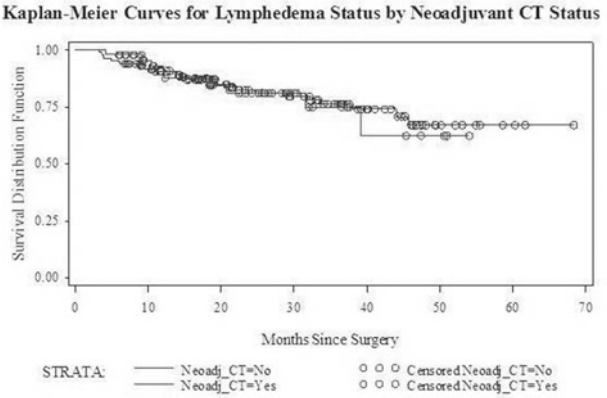
Table 1: Patient characteristics

	DCIS (n=41)	IBC (n=120)
Median age, y (range)	55.0 (33-74)	53.0 (26-79)
Tumour size, mm (range)	48 (1-135)	16.0 (1.4-200)
Primary tumour. N (%)		
Tis	41 (100)	0
T1	0	62 (53.3)
T2	0	35 (29.2)
T3	0	8 (6.7)
T4	0	1 (0.8)
unknown	0	12 (10.1)
Grade		
1	7	23
2	10	41
3	20	43
Unknown	4	14
Multi-		
Centric	4	9
Focal	11	51
Centric/focal	1	12
Unifocal	24	42
Unknown	1	6
Nodal Status		
Negative	38	81
Positive	0	37
Unknown	3	2
Estrogen receptor status		
+	0	83
-	41	35
Adjuvant therapy		
Neo-adj. chemotherapy	3	14
Adjuvant chemotherapy	0	59
Hormonal therapy	3	61
Radiation therapy	4	21
Herceptin	2	20

P147

Does Neoadjuvant Chemotherapy Reduce the Risk of Lymphedema in Patients with Node Positive Breast Cancer? M. Specht,* C. Miller, N. Horick, M. Skolny, J. O'Toole, B.L. Smith, A. Taghian. *Massachusetts General Hospital, Boston, MA.*

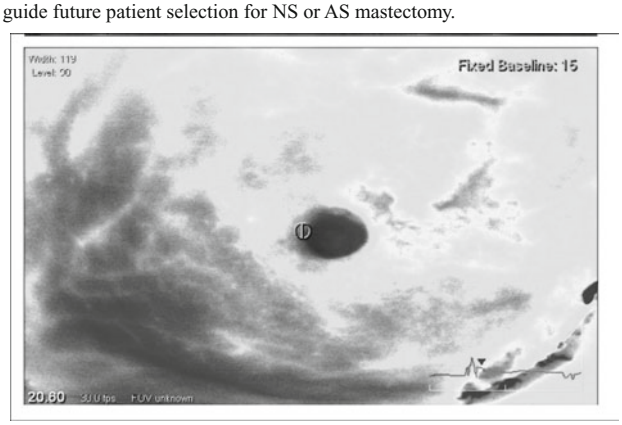
Introduction: Axillary lymph node dissection (ALND) is recommended for patients with clinically node positive breast cancer and carries a risk of lymphedema as high as 30%. Studies have demonstrated that neoadjuvant chemotherapy can reduce the number of positive lymph nodes. However, there is little data regarding whether this reduces the risk of lymphedema. We sought to determine if neoadjuvant chemotherapy reduced the risk of developing lymphedema in patients undergoing ALND for node positive breast cancer. Methods: 184 patients with breast cancer who underwent ALND and chemotherapy from 2005 to 2010 were divided into two groups, 50/184 (27%) patients had neoadjuvant chemotherapy, and 134/184 (73%) had adjuvant chemotherapy. Prospective arm volumes were measured via perometry at diagnosis, pre and post-op, and at 4-7 month intervals. Arm volume changes were quantified as Relative Volume Change (RVC) between the treated (T) and non-treated (N) arm as compared to baseline measurement(b): RVC=(T/N)/(Tb/Nb)-1. Lymphedema was defined as RVC ≥10%, >3 months from surgery. Kaplan-Meier curves were constructed and univariate Cox proportional hazards regressions were used to identify risk factors for lymphedema. Results: There was no difference in the development of moderate lymphedema, 9/50 (18%) neoadjuvant patients compared with 27/134 (20%) adjuvant patients developed RVC ≥ 10%. (Figure) Patients undergoing neoadjuvant compared with adjuvant chemotherapy had fewer positive lymph nodes, medians were 1 vs. 2 respectively (p=0.01). Increased BMI at diagnosis was significantly associated with increased risk of lymphedema (p=0.0004). Conclusion: Neoadjuvant chemotherapy does not reduce the risk of lymphedema after ALND in node positive breast cancer patients. Therefore, alternatives to ALND and other strategies to prevent lymphedema are required for patients with Stage II-III breast cancer.



P148

Determining Adequate Nipple Areolar Complex Perfusion in Breast Cancer Related Mastectomies A. Kieryn,* M. Dua, J. Paro, S. Meyer, G. Gurtner, I. Wapnir. *Stanford, Stanford, CA.*

Introduction: The use of nipple-sparing (NS) and areolar-sparing (AS) mastectomies accompanying immediate reconstruction is increasing. It is well know that significant post-mastectomy and breast reconstruction complications can include skin necrosis and infections. Published incidences of complications range between 10% and 40% and are predominantly associated with malperfusion of mastectomy skin flaps. The purpose of this study is to determine if perfusion patterns to the nipple areolar complex (NAC) contribute to post-mastectomy tissue viability. Methods: Ten consecutive patients with in situ or invasive cancers underwent 15 NS or AS mastectomies (5 unilateral and 5 bilateral). We performed pre and post-mastectomy imaging of NAC perfusion using fluorescent indocyanine green (IC-Green©) dye injection and an infrared (SPY© imaging) camera to record real time perfusion. NAC perfusion was classified as filling centrally (N1), peripherally (N2), or both (N3). Areas of inadequate perfusion were identified intraoperatively and either removed or monitored further postoperatively. Results: The NAC was well perfused after breast tissue removal in 8 of the 15 cases. Six of the 8 (75%) had pre-mastectomy N2 and 2 of the 8 (25%) N3 blood flow patterns to the nipple. Ischemia was identified after breast tissue removal on SPY© imaging in the remaining 7 breasts. Five of these (71.4%) demonstrated pre-mastectomy N1 and 2 (28.6%) N3 perfusion patterns. None of the 7 cases with ischemia had an N2 NAC perfusion pattern prior to breast tissue removal. Conclusion: Based on our results, peripheral perfusion patterns are associated with adequate perfusion of the NAC after mastectomy. Central perfusion patterns to the NAC reliant on the underlying breast tissue for blood flow showed ischemia immediately post mastectomy. Further assessment of preoperative perfusion patterns to the NAC may guide future patient selection for NS or AS mastectomy.



Peripheral NAC Perfusion as seen with SPY© Imaging

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Breast Reconstruction in the Insured and Underinsured Population: A Single Institution Approach T.L. Shell,* E. Feliberti, R. Britt, C.N. Jay, R. Perry, L. Viennas, D. Trzcinski. *Surgery, EVMS, Norfolk, VA.*

Introduction: The rates of breast reconstruction among insured patients remain as low as 20-30%. However, breast reconstruction rates in the underinsured population are even lower, estimated at 5-8%. This study measured the impact of plastic surgery as part of the multidisciplinary team in breast cancer patients treated with mastectomy. Methods: In this retrospective chart review at a single institution, 95 mastectomy patients were identified from both a private clinic and a low-income clinic from January 1, 2008 through March 31, 2011. This subset of patients was further divided by history of breast reconstruction versus no reconstruction. We then did a racial comparison amongst the reconstructed patients in both the private clinic and underinsured clinic. Mastectomy patients were also analyzed in terms of age by decade and whether they had breast reconstruction or not. Results: Of the 95 mastectomy patients, 85% (n=81) are from the insured population and 15% (n=14) are from the underinsured population. 57% of the total mastectomy patients (n=54) underwent breast reconstruction. In comparing the insured versus underinsured population, 58% of the insured mastectomy patients compared to 42% of uninsured mastectomy patients underwent breast reconstruction (n=48 insured, n=6 uninsured, p=0.253). There was no difference in breast reconstruction rates between Caucasian and African American women (60% vs. 52%, p=NS). Furthermore, we discovered that 69% (n=43) of our patients under the age of 60 opted for breast reconstruction, while only 27% (n=9) of patients over the age of 60 had breast reconstruction. No mastectomy patients over the age of 70 underwent breast reconstruction. Conclusion: Inclusion of plastic surgery in the multidisciplinary breast cancer team can result in improved breast reconstruction rates. In addition this can diminish disparities in reconstruction rates in minority and underinsured women.

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Breast Cancer Screening in a Socioeconomically Underprivileged Patient Population Served by A State-funded Program T. Schwartz,* C. Doherty, A. Parker, P. Hunborg, P. Petruska, V. Mark, H. Eddy. *Theresa Schwartz, Saint Louis University, St. Louis, MO.*

Background: Disparities in receipt of cancer-screening services based on insurance coverage have been well documented. Uninsured patients have been shown to present with more advanced disease and a higher adjusted risk of death compared to patients with private insurance. 15% of adult women in the state of Missouri lack health insurance. A state-funded program has been developed that offers free screening mammograms to age and income eligible women. This study sought to investigate the patient demographics of the women enrolled in this program as well as the incidence of breast cancer diagnoses in this socioeconomically underprivileged cohort. Methods: A retrospective chart review was conducted of all women enrolled in the Show Me Healthy Women program at St. Louis University since its inception in 2009. Patient demographics, imaging findings and biopsy results were assessed. Results: 176 women were eligible for enrollment in this program from September 2009 to August 2011. The median age was 47.3 (range 15-65). 82 (46.5%) were African American, 66 (37.5%) were Hispanic and 20 (11.4%) were Caucasian. 128 (73%) underwent screening mammograms with 35 (27%) of these patients requiring diagnostic imaging. 25 patients (14%) required a biopsy with 6 of the 25 (24%) resulting in an invasive carcinoma. The median number of days from imaging to tissue diagnosis was 25 days (range 0-113) for all patients requiring a biopsy and 0 days for patients with cancer (range 0-35). Of the 6 patients with cancer, the median age was 47.3 years. 4 were African American and 2 were Hispanic. Four out of the 6 were diagnosed following their baseline mammogram, resulting in a 3% incidence rate after initial mammogram. Four (67%) were grade 3. All tumors were larger than 2 cm, with 3 being ER, PR and HER2 negative. Four patients were node positive. Conclusions: Access to preventative cancer screening protocols is limited in women who lack health insurance. Free cancer screening programs may have prognostic benefits for women in this socioeconomic cohort. Further studies need to be conducted to investigate any differences in outcome in women receiving these services.

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Surgical Practice Patterns of Metachronous Bilateral Breast Cancer L.A. Gutierrez,* N.L. Watroba, K.S. May, K.M. Attwood, A. Miller, S.B. Edge, S. Kumar. *Roswell Park Cancer Institute, Buffalo, NY.*

Background: About 10% of women with breast cancer will develop a contralateral breast cancer during their lifetime. There is limited literature defining the type of local therapy selected for the second cancer and factors that influence this choice. The objective of this study is to examine the clinical and pathologic factors associated with the local therapy of women with metachronous bilateral breast cancer. Methods: From July 1997-December 2010, 85 patients at our institution were diagnosed with metachronous bilateral breast cancer (defined as 6 months or greater between diagnoses, median 43.1 months) and were treated with either breast conserving therapy (BCT) or mastectomy. Demographic and clinicopathologic characteristics, along with the type of surgical management of the second cancer were examined. Results: The type of surgery for the first and second cancer is shown in the table. Overall, 60 of 85 patients had the same local therapy for both cancers. Women treated with mastectomy for both cancers were younger (p<.001) and less likely to have radiation at their second surgery. They had a higher level of education (p=.014). Women who had BCS for both cancers were older and more likely to receive radiation (p=.014). Based on the surgery for the second cancer, mastectomy was associated with younger age, higher level of education, and use of chemotherapy. Use of BCS was associated with higher body mass index and use of radiation. Conclusions: Patients with metachronous BBC are likely to undergo the same type of surgical treatment for each breast cancer diagnosis. Use of mastectomy was associated with younger age and higher level of education. Further study into additional factors that may influence surgical decision making is warranted.

		Second Surgery			
		Lumpectomy	Mastectomy	Overall	
Overall First Surgery	N	56(65.9%)	29(34.1%)	85(100%)	P-Value
	Lumpectomy	45(80.4%)	14(48.3%)	59(69.4%)	.003
	Mastectomy	11(19.6%)	15(51.7%)	26(30.6%)	

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Utilization of Mastectomy and Reconstruction in the Outpatient Setting L. Kruper,* X. Xu, S.L. Chen, L. Bernstein, K. Henderson. *City of Hope, Duarte, CA.*

Background: Reconstruction rates after mastectomy have been reported ranging from 25%-40%, however, most studies have focused on patients treated in an inpatient setting. We sought to determine the utilization of outpatient mastectomy and use of breast reconstruction in Southern California. Methods: Postmastectomy reconstruction rates were determined from the California Office of Statewide Health Planning and Development (OSHPD) outpatient database from 2006-2009 using Current Procedural Terminology (CPT) codes. Similarly, postmastectomy reconstruction rates were determined from the OSHPD inpatient database using International Classification of Diseases (ICD-9) codes. Reconstruction rates were compared between the inpatient and outpatient setting. For the outpatient setting, univariate and multivariate odds ratios (OR) with 95% confidence intervals (CI) were estimated for relative odds of immediate reconstruction versus mastectomy only for calendar year, age, and type of hospital. Results: The percentage of patients undergoing outpatient mastectomy ranged from 20.4% to 23.9% of the total number of all patients undergoing mastectomy. While inpatient mastectomies with immediate reconstruction increased from 29.2% to 41.6%, the proportion of outpatients undergoing reconstruction only rose from 7.7% to 10.3%. The majority of outpatient mastectomies were performed at non-teaching hospitals and hospitals which were not designated cancer centers (91.2%). In multivariate analysis, age and type of hospital were significantly associated with the use of reconstruction in the outpatient setting. Conclusions: A substantial number of patients undergo outpatient mastectomy with low rates of reconstruction. While the choice of an outpatient mastectomy may certainly represent a selection bias for those not choosing reconstruction, an increase in the use of outpatient mastectomy may result in decreases in the use of postmastectomy reconstruction.

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Use of Complementary and Alternative Medicine by Breast Cancer Patients in the Netherlands M. Martens,[1]* L.M. Van Roozendaal,[1] L.J. Schouten,[2] R.J. Hermans,[3] A. Bast,[3] M.P. Weijenberg,[2] M.L. Smidt.[1] *1. Surgery, Maastricht University Medical Center, Maastricht, Netherlands; 2. Epidemiology, Maastricht University Medical Center, Maastricht, Netherlands; 3. Farmacology, Maastricht University Medical Center, Maastricht, Netherlands.*

Introduction: Breast cancer patients are known to be frequent users of Complementary and Alternative Medicine (CAM) in de USA and Great-Britain. Several studies have shown interactions between natural CAM and conventional cancer treatment. The aim of this study was to determine the prevalence and predictors of use of CAM by breast cancer patients in the Netherlands, and to explore the association between CAM therapy use, quality of life (QOL), trust in conventional therapies, and feelings of self-control over health and illness. Methods: A questionnaire assessing the use of CAM, focusing on natural products, was sent prospectively to a cohort of 241 breast cancer patients within 2 weeks after diagnosis in the period from July 2010 to July 2011. Clinical variables were obtained from medical records. Descriptive statistics, t-tests and logistic regression analyses were conducted. Results: The response rate was 48.1%. Of the 116 respondents 44.8% used CAM. Vitamins and minerals were the most common (52.0%) used CAM product. Patients usually started with CAM on their own initiative and the most common reason to use CAM was to stimulate the immune system (53.8%). 65.4% did not report CAM use to the physician, usually because patients thought it was unimportant (51.6%). Most CAM users (88.0%) thought CAM was effective. There was no significant difference in age (p=0.628), educational level (p=0.228), relationship status (p=0.972), having children (p=0.204), BMI (p=0.026), or smoking (p=0.145) between CAM-users and non-users. More CAM-users drank more than 1 alcohol consumption per week than non-users (OR 2.77, p=0.010). No statistical significant difference existed in faith in conventional treatment (p=0.635) or QOL (p=0.355) The Multidimensional Health Locus of Control (MHLC), for determining the locus of control over a patient's health or illness showed no significant difference between the two groups. Conclusion: CAM use appeared common among recently diagnosed breast cancer patients in the Netherlands. Since clinically significant drug interactions have been described for CAM, physicians and other health care providers should discuss this topic with their patients.

P154

Effect of Experience and Specialization on Breast Conservation Therapy M.M. Fillion,* L.M. James, H.S. Nelson. *University of Tennesse Graduate School of Medicine, Knoxville, TN.*

INTRODUCTION General surgeons and specialists may perform breast conservation therapy as a treatment for breast cancer. Hookwires may aid in successful conservation. We hypothesized that years of experience and specialization would have no difference on margin status and breast tissue resected. METHODS After IRB approval, a retrospective review of 201 patients with breast cancer who were treated with hookwire guided partial mastectomy was undertaken at our institution from 2004 to 2008. Surgeons were separated into categories based on 1) years of experience: less than 10 years (LE) or greater than 10 years (GE) from residency and 2) specialty: general surgeons (GS) or surgical oncologists (SO). Margins were considered positive if tumor cells were present at inked borders. The largest tumor dimension and volume resected were calculated from pathology reports. RESULTS There were 5 GS and 5 SO performing this procedure; 4 GE and 6 LE. There were 162 patients in GE cohort and 39 patients in LE cohort. GE and LE each had 23% positive margins and 34% and 33% re-operation respectively (p=1). There was no difference type of cancer, the size of the lesion or the amount of breast tissue resected between the two experience groups of surgeons. There were 142 patients operated on by SO and 59 patients operated by GS. GS had 39% positive margins and 49% re-operation as compared to SO with 17% positive margin and 27% re-operation (p=0.0016 and p=0.2263). Specialists resected more breast tissue, 172 cm3, as compared to GS, 120cm3 (p=0.0036). There was no difference in the type or size of cancer in patients operated on by GS and SO. CONCLUSIONS Specialization resulted in improved negative margin status. However, while fewer positive margins were in the SO cohort; these surgeons resected more breast tissue at the initial operation. Surgeons need to be aware of their own outcomes in the era of performance evaluation.

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Immediate Breast Reconstruction and Radiation Treatment: Lower the Risk of Complication by Arranging the Timing of Radiation R. In,[1]* Y. Iwahira,[2] A. Yoshida,[1] N. Hayashi,[1] H. Yagata,[1] K. Sekiguchi,[1] H. Yamauchi.[1] *1. Breast Surgery, St.Luke's Inter National Hospital, Tokyo, Japan; 2. Breast Surgery Clinic, Tokyo, Japan.*

Background The immediate breast reconstruction with tissue expander and implant is becoming the main reconstructive procedure and has been increasing number of patients who require the radiotherapy with breast reconstruction. However, radiation treatment (Rtx) to reconstructed breast is known as containing the risk of severe complication. Methods Three hundred sixty-one patients underwent immediate breast reconstruction after mastectomy between January 2007 and December 2010. Among those, we compared complication rates between with and without Rtx. Results Total 26 patients received Rtx for breast before or after reconstruction, while 333 patients who underwent breast immediate reconstruction without radiotherapy. Total 21 patients (5.8 %) required re-operation; 17 out of 316 cases (5.1 %) reconstructed breasts without radiotherapy, 4 out of 22 cases (15.4 %) reconstructed breasts with Rtx. Higher re-operation rates was observed in patients with Rtx than those without Rtx (P=0.055). In addition, there is the trend of higher complication rates in patients who underwent Rtx followed by skin expansion (4 of 15, 26.4%) than that in patients underwent skin expansion followed by Rtx (none of 11, 0.0%). Conclusions Radiation for reconstructed breast may contribute complication risk. However, although further studies including cosmetic outcomes is required, we may reduce the risk of complication if skin expansion and implant replacement are performed prior to the Rtx.

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Complications of Immediate Breast Reconstruction after Skin Sparing Mastectomy Do Not Cause Delay of Onset of Adjuvant Chemo- or Radiation Therapy O. Van Waardhuizen,[1] M. Martens,[1] D. Van Mierlo,[1] R. Schipper,[1]* M. Lobbes,[2] S. Tuinder,[3] E. Heuts,[1] M. Smidt.[1] *1. Maastricht University Medical Center, department of Surgery, Maastricht, Netherlands; 2. Maastricht University Medical Center, department of Radiology, Maastricht, Netherlands; 3. Maastricht University Medical Center, department of Plastic Surgery, Maastricht, Netherlands.*

Background The incidence of immediate breast reconstruction (IBR) after a breast cancer operation is rising, offering patients advantages in terms of QOL. This study only concerns IBR after skin-sparing mastectomy (SSM). Safety of this procedure is a critical issue and can be measured in terms of local recurrence. Published studies show no rise though compared to the standard mastectomy. Another consequence could be the higher risk for complications and therefore the possible delay in the start of any adjuvant therapy. The aim of this study was to evaluate the incidence of complications after SSM with IBR in patients treated for invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS), whom received adjuvant chemo- or radiation therapy in a dedicated institute and to assess whether they affect the interval between surgery and adjuvant therapy. Methods - Data of all SSM with IBR patients were retro- and prospectively collected between 2004 and 2011. The database consists of 251 SSM with IBR. Only patients treated with adjuvant chemotherapy and/or radiation therapy were included (n=60); 95% (n=57) with IBC and 5% (n=3) with DCIS. Patients characteristics are collected in Table 1. Almost all SSM and IBR were performed by a dedicated team of oncologic and plastic surgeons. Results Some form of flap reconstruction was performed in 19 breast of the uncomplicated group and in 7 breast of the group with complications. A tissue expander or direct prosthesis was placed in 35 and 15 breasts, respectively. The number of patients with complications was 16 (26.7%). In 9 patients, the complications of surgery occurred before the start of adjuvant therapy; in 7 during adjuvant therapy. In none of these patients, adjuvant therapy was paused due to complications. The mean number of days between the IBR and the start of adjuvant chemo- or radiation therapy was 28.6 in the group with complications. For the uncomplicated group, this period was 32.6 days. However, this is not significant (p=0.46). Conclusions - Complications associated with SSM with IBR do not delay the start of indicated adjuvant chemo- or radiation therapy.

Patient and tumour characteristics of 60 patients

SSM with IBR with adjuvant therapy		Without complications	With complications	p-value
Patients, n		44	16	
Mean age, y (range)		48.4 (25-66)	48.4 (29-67)	0.991
BMI (kg/m2)		23.9 (16-30)	24.0 (19-33)	0.735
Smoking (%)		27.3	12.5	
Mean Tumor size, mm (range)		27.2 (0-200)	25.2 (0-70)	
Primary tumour (%)				
	T0	3 (7)	1 (6.3)	
	Tis	3 (7)	0	
	T1	17 (39.5)	6 (37.5)	
	T2	15 (34.9)	7 (43.8)	
	T3	4 (9.3)	2 (12.5)	
	T4	1 (2.3)	0	
Nodal status				
	N -	24(55.8)	8 (50)	
	N +	19 (44.2)	8 (50)	
Neo-adjuvant chemotherapy		9	1	
Number of breast reconstructions, n		54	22	
	Unilateral	32	10	
	Bilateral	11	6	
Complications, n (%)				
	Flapnecrosis		4 (25)	
	Wound infection		10 (62.5)	
	Haemorrhage		6 (37.5)	

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Residual Disease in Re-Excision Partial Mastectomy (PM) for Positive Margins in Breast Conservation Therapy A.M. Deladisma,* P. Arriagada, L.T. Greer, M. Rosman, C. Mylander, R.R. Buras, L. Tafra, W. Liang. *Breast Center, Anne Arundel Medical Center, Annapolis, MD.*

Background: Obtaining tumor-free margins is a goal of breast conservation therapy to reduce the risk of local recurrence of breast cancer. We examined the relationship between margin size and presence of residual disease to determine if there is an acceptable threshold for defining a positive margin below 2 mm. Methods: A retrospective chart review was conducted of all PM done for re-excision of positive (on ink to < 2 mm) margins between May 2007 and April 2011. Data extracted included patient age, distance of tumor to the margin at initial PM (on ink or 0, >0 to ≤1 mm, >1 to <2 mm), tumor type at margin (invasive only, any DCIS), and presence of residual disease at re-excision. Proportion of patients with residual disease and 95% confidence intervals (CI) were calculated. Results: Two hundred three PM were done for re-excision of positive margins. At initial PM, 99 (48.8%) patients had tumor on ink at the closest margin, 68 (33.5%) had tumor within 1 mm, and 36 (17.7%) within 1 to 2 mm. Sixty-nine patients had only invasive disease at the margin (34.0%) and 134 had DCIS (66.0%). Residual tumor was found in 75 (36.9%) patients. Residual tumor was not significantly associated with patient age or type of tumor at the margin. By margin size, tumor was found in 49 (49.5%, 39.9-59.2%) of on ink margins, 18 (26.5%, 17.4-38.0%) of >0 to ≤1 mm margins, and 8 (22.2%, 11.7-38.1%) of >1 to <2 mm margins. Residual tumor was significantly more likely to be present at re-excision in specimens with tumor on ink compared to >0 to ≤1 mm or >1mm to <2 mm. This relationship did not persist on stratified analysis by type of tumor at the margin (table). Conclusion: Among patients with DCIS at the margin, there is a trend toward increased probability of finding residual disease at re-excision PM with shorter distance of tumor to margin at initial PM. Although decreasing the threshold for a positive margin would reduce the number of re-operations, a considerable number of women would be left with residual disease. A margin threshold less than 2 mm can only be justified if it can be demonstrated that adjuvant treatment would prevent recurrence from any residual tumor.

Presence of Residual Disease by Distance of Tumor to the Margin Stratified by Type of Tumor at Positive Margin

Distance of Tumor to Margin on PM (mm)	Invasive Only at Margin of PM (n=69)			DCIS at Margin of PM (n=134)		
	No Residual Tumor Present	Residual Tumor Present	% (95% CI)	No Residual Tumor Present	Residual Tumor Present	% (95% CI)
On Ink (0)	17	10	37.0 (21.5-55.8)	33	39	54.2 (42.7-65.2)
>0 to ≤1	19	3	13.6 (4.8-33.3)	31	15	32.6 (20.9-47.0)
>1 to <2	15	5	25.0 (11.2-46.9)	13	3	18.8 (6.6-43.0)
	51	18		77	57	

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Metastatic Ductal Carcinoma-in-situ with No Evidence of Locoregional Recurrence: How Rare is Rare? K. Ching,* P. Tartter, K. Boachie-Adjei, S. Rosenbaum Smith, A. Estabrook. *Surgery, St. Luke's-Roosevelt Hospital, New York, NY.*

Introduction: Ductal carcinoma-in-situ (DCIS) is characterized by confinement of tumor cells within an intact basement membrane theoretically excluding the possibility of metastases. The observation of distant metastasis (DM) after DCIS without an intervening invasive locoregional recurrence (LRR) defies simple explanation. We propose a study that may identify a subset of patients with DCIS who will develop DM without any evidence of LRR. Methods: A retrospective review of a multi-center Breast Cancer Database was done to identify all cases with DCIS from January 2000 to December 2010. Of these, cases with LRR alone, LRR with DM, and DM alone with no evidence of LRR were identified. Paper charts and electronic medical records were reviewed as well. Clinical, biochemical and pathological factors were examined and analyzed. Data analysis was done through the use of SSPS (Statistical Package for the Social Sciences) software. This study was approved by the Institution's IRB. Results: 907 cases with DCIS were identified. Mean age of the population was 56 years (range 25-99 years). There were 905 cases from female patients, and 2 from male patients. Of the 907, 81 cases (0.09%) had a recurrence. Mean time to follow-up is 5 years (median 3.89 years). All of the recurrent cases were female patients. Of these 81 cases, 75 (93%) had only LRR, 4 (0.05%) had only DM, and 2 (0.02%) had both LRR and DM at the time of recurrence. All 4 cases with only DM were from female patients – 2 Caucasian and 2 African-American with mean age 46 years. Their initial DCIS were all hormone receptor positive and none had any comedo necrosis. Two cases were managed by mastectomy, the other two by breast conservation therapy (BCT). Distant metastatic sites included the liver, supraclavicular node, and bone. Mean time to distant recurrence was 2.67 years from initial diagnosis of DCIS. Mean total follow-up for the 4 cases is 5.6 years. Conclusions: Distant metastasis after DCIS is rare. There was no observed dominant patient or tumor factor that can predict a distant recurrence after an adequately treated DCIS. Young age at initial DCIS seems to confer a negative prognostic value.

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KRAS Mutation is a Poor Prognostic Factor in Patients undergoing Hepatic Resection for Metastatic Colorectal Cancer R.D. Aufforth,[1]* J.J. Baker,[1] J. Auman,[1] R. Eil,[2] H. McLeod,[1] H. Kim,[1] M.O. Meyers,[1] B.F. Calvo,[1] J. Yeh.[1] *1. University of North Carolina, Chapel Hill, NC; 2. Oregon Health Science University, Portland, OR.*

Background: It is well known that *KRAS* mutations limit the efficacy of anti-EGFR therapy in patients with metastatic colorectal cancer (mCRC). However the role of *KRAS* mutations in patients who undergo a curative liver resection for mCRC is less clear. The purpose of our study was to evaluate the relationship between *KRAS* mutation status and survival in this patient population. Methods: We examined an IRB approved tissue repository and retrospective database of 129 patients from 1998-2010 who underwent curative liver resection for mCRC. Tumors were sequenced for *KRAS* codons 12, 13, and 61 mutations using pyrosequencing. Overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression method. Results: The median follow-up for our cohort was 20.4mo (0.4-112). Mean age was 61.4±12.3. Prior to surgical resection 55 (43%) patients received chemotherapy. 35 (27%) tumors were *KRAS* mutant (mt), 83 (64%) were wild-type (wt), and 11 (9%) were not characterized. Median OS for *KRAS* wt patients was 40.3mo vs. 27.1mo for *KRAS* mt patients (p=0.046). Median DFS for *KRAS* wt was 13.6mo vs. 7.7mo for *KRAS* mt patients (p=0.037). 8 patients received cetuximab post–operatively. Cetuximab status was unknown in 50 patients. When we excluded those treated with cetuximab, the median OS was 40mo for *KRAS* wt vs. 25mo for *KRAS* mt patients (p=0.007). There were no differences in OS or DFS in patients who received cetuximab (p=0.7). In a multivariable model with pre-operative chemotherapy (p=0.2), extent of resection (p=0.053), and cetuximab therapy (p=0.7), the presence of *KRAS* mutation was independently associated with poor prognosis (HR=2.7 [1.3-5.5]). Conclusions: In patients undergoing curative liver resection for mCRC, *KRAS* mutation status is independently predictive of a worse outcome regardless of cetuximab therapy. *KRAS* status may be associated with more aggressive tumor biology. Our data supports the critical need to define *KRAS* muta-

tion status and to develop therapies against *KRAS* and its downstream effectors.

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Long-term Outcome of Locally Advanced Rectal Cancer in Relation to Pathological Response in Mesorectal Lymph Nodes after Neoadjuvant Chemoradiation: Implications for Surgical Treatment

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Introduction: In locally advanced rectal cancer, neoadjuvant chemoradiation (CRT) determines tumor regression on mesorectal lymph nodes as on primary tumor. This contributes to the rational for exploring local excision surgical strategies in patients with primary tumor pathological complete response (pCR). The aim of this study was to analyze long-term outcome of locally advanced rectal cancer patients in relation to pathological response in primary tumor and in mesorectal lymph nodes. Methods: Clinicopathological and outcome data were retrieved from our Institutional prospective rectal cancer database. Survival analysis was performed with Kaplan-Meier method, and hazard ratios calculated with Cox proportional model. Results: Study population comprised 143 patients (89 men, 54 women; median age 63 yrs, range 25-88) with locally advanced rectal adenocarcinoma (54 cT3N0, 65 cT3N1, 11 cT4N0, 13 cT4N1) treated by CRT followed by surgery including total mesorectal excision (118 LAR, 35 APR) at our Institution between 1996 and 2009. At pathology, primary tumor pCR (ypT0) was observed in 34 (23.8%) cases. Median number of examined lymph nodes was 14. Metastatic lymph nodes were detected in 37 (47.4%) cN1 cases compared to none in cN0 ($p<0.001$). In cN1 patients, metastatic lymph nodes were detected in 5 out of 19 ypT0 cases (26.3%). During a median follow-up of 60.2 months, 48 (33.6%) patients had recurrent disease, and 36 (25.2%) died of disease. Five-year DSS was 92.0% in ypT0N0 patients compared to 60.0% in ypT0N1 ($p=0.019$). Multivariate analysis, demonstrated that metastatic lymph nodes at pathology was a negative independent prognostic factor with an additional risk of dying of disease of 3.74 ($p=0.010$) (Table). Conclusions: Locally advanced rectal cancer patients initially staged as cN-positive have a considerable risk of harbouring metastatic mesorectal lymph nodes, which is a potent negative prognostic factor. Therefore, these patients should be excluded from investigational studies exploring local excision surgical approach in patients with primary tumor pCR after CRT.

Multivariate analysis of clinical and pathological prognostic factors in 143 patients with locally advanced rectal cancer treated by neoadjuvant chemoradiation and radical surgery including total mesorectal excision.

	LRF			MFS			DSS		
	5-yr %	HR (95% CI)	p	5-yr %	HR (95% CI)	p	5-yr %	HR (95% CI)	p
cT									
cT3	84.0	1		82.8	1		82.0		
cT4	49.5	3.6 (1.6-8.1)	0.001	54.7	2.85 (1.3-6.1)	0.007	54.0	3.87 (1.8-8.0)	<0.001
cN									
cN0	84.1	1		78.2	1		87.3	1	
cN1	75.1	1.55 (0.5-4.1)	0.388	78.2	0.26 (0.1-1.1)	0.071	67.8	1.23 (0.4-3.5)	0.702
ypT									
ypT0	85.0	1		91.2	1		87.1	1	
ypT1-4	77.1	1.55 (0.5-4.1)	0.587	73.8	1.73 (0.6-5.0)	0.313	74.4	2.47 (0.8-7.1)	0.091
ypN									
ypN0	83.1	1		84.3	1		87.6	1	
ypN1	66.7	1.64 (0.6-4.4)	0.326	57.7	7.36 (1.6-33.2)	0.009	45.5	3.74 (1.3-10.2)	0.010

LRF, local recurrence free survival; MFS, metastasis free survival; DSS, disease specific survival; HR, hazard ratio.

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Robotic Rectal Resection for Cancer: A Prospective Analysis of Clinical and Oncological Outcomes in 84 Patients P. Bianchi,* W. Petz, L. Casali, D. Belotti, M. Parodi. *Unit of Minimally Invasive Surgery, European Institute of Oncology, Milano, Italy.*

Introduction. Robotic surgical approach to the lower pelvis may increase the precision of rectal dissection and overcome technical difficulties of conventional laparoscopy. This prospective study evaluate technical aspects, clinical outcomes and oncological results of 84 patients. Methods. From August 2008 to September 2011, 84 patients underwent robotic-assisted rectal resection for adenocarcinoma. In patients with locally-advanced non metastatic tumor pre operative chemo-radiotherapy (CRT) was administered. Sphincter preservation was realized every time the lesion was localized at least 3 cm above the anal verge. Results. Median age was 64 years (range 33-85), median body mass index was 25 kg/m2. Twenty-eight patients (33%) received a preoperative CRT. Surgical procedure was in 16 (19%) cases an abdominoperineal resection, in 68 (81%) cases an anterior resection. A temporary ileostomy was realized in 28 (41%) patients. Splenic flexure mobilization was realized laparoscopically in 48 (70%) cases and with fully robotic technique in 20 (30%) cases. Median surgical time was 245 minutes. No conversion to open surgery was necessary. Major complications requiring reoperation occurred in 5 patients (5.9%). Median hospital stay was 6 days. Mean number of harvested lymph nodes was 22 (4-51), median distal resection margin in patients who underwent anterior resection was 4 cm (0.5-8), in 82/84 patients circumferential margin was >1 mm. American Joint Committee on Cancer stage was 0 in 17 patients (20%), I in 16 patients (19%), II in 18 (21%), III in 27 (32%) and IV in 6 patients (7%). At a median follow up of 12 months, overall survival rate is 95% and recurrence rate is 3%. Conclusions. Robotic-assisted surgery of the rectum is a safe and feasible technique without conversion to open surgery and with clinical and oncological results comparable to open and laparoscopic surgery. Further comparative studies are necessary to evaluate potential advantages of robotic technique in rectal cancer.

P162

Clinical Significance of NEK2 Expression in Colorectal Cancer Cases T. Yusuke,[1]* I. Masahisa,[1] G. Sawada,[1] R. Kogo,[1] N. Nishida,[1] T. Akagi,[1] T. Iwaya,[1] T. Sudo,[1] F. Tanaka,[1] K. Shibata,[1] K. Mimori,[1] M. Mori.[2] *1. Department of Surgery, Kyushu University Beppu Hospital, Beppu, Oita, Japan; 2. Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.*

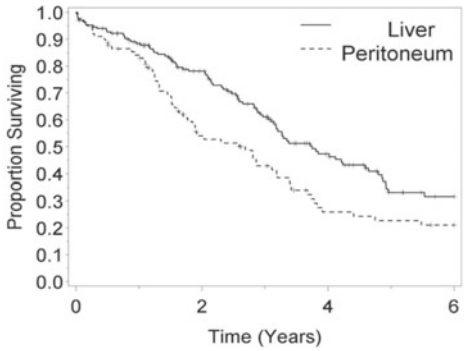
INRODUCTION: NEK2 (NIMA-related kinase 2) has a role in cell division and mitotic regulation by centrosome splitting. It is reported that NEK2 is involved in genesis or progression of cancer and abnormally expressed in a wide variety of human cancers, including colorectal cancer (CRC). We investigated the clinical significance of NEK2 in CRC cases, in particular focusing on miR-128 which hypothetically targets at NEK2. METHODS: We examined NEK2 mRNA levels in 180 CRC samples and miR-128 levels in 136 samples by quantitative real-time PCR and analyzed the association among NEK2 mRNA levels, miR-128 levels, and clinicopathologic factors and prognosis. We performed luciferase assay to validate the relationship between NEK2 and miR-128 in HT29 and RKO cell lines. RESULTS: 180 paired primary tumor samples were studied using quantitative real-time RT-PCR. NEK2 mRNA expression was significantly higher in tumor than in normal tissue ($P < 0.0001$). Clinicopathological evaluation showed statistically significant differences between groups with high and low NEK2 expression (classified as having expression levels higher or lower than the median value, respectively). Significant between-group differences were observed in serosal invasion (Student's t-test, $p=0.024$), lymph node metastasis ($P = 0.005$), lymphatic invasion ($P = 0.018$) and peritoneal dissemination ($P = 0.004$). Furthermore, the high-NEK2 expression group had a significantly poorer prognosis than did the low expression group ($P = 0.014$). Multivariate analysis indicated that high NEK2 expression was an independent prognostic factor for survival. As for miR-128 expression, there was no significant difference in clinicophathological analysis, but quantitative real-time PCR indicated that the high miR-128 expression group had significantly lower NEK2 expression than the low miR-128 expression group. Luciferase assay validated the inhibition of NEK2 expression by miR-128. CONCLUSIONS: Our data showed that NEK2 could be an important indicator for colorecral cancer patients and was regulated by NEK2. We expected that the development of molecular target treatment to inhibit NEK2 directly or miR-128 mimic administration.

P163

Decreased Survival after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Compared to Hepatic Resection for Metastatic Colorectal Cancer A. Blackham,* G.B. Russell, J.H. Stewart, K. Votanopoulos, E.A. Levine, P. Shen. *Wake Forest School of Medicine, Winston-Salem, NC.*

Introduction: Surgical resection of peritoneal metastases (PM) from colorectal cancer has been reported to yield outcomes similar to liver resection for

hepatic metastases (HM). However recent data suggests PM may have a worse prognosis than other metastatic sites. Methods: A retrospective review of metastatic colorectal cancer patients obtained from prospective databases (1992-2010) comparing liver resection for HM to cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for PM. Results: 181 patients underwent hepatic resection and 182 patients underwent CS/HIPEC with a median follow-up of 55 and 106 months respectively. A margin-negative resection was obtained in 168 (93%) hepatic resections, while 89 patients (49%) with PM had complete cytorection of all gross disease (R0/R1). A comparison of these two groups demonstrated significant differences in age, pre-operative chemotherapy and performance status. Disease-free median survival was 15.2 months after hepatic resection and 9.9 months after CS/ HIPEC (p=0.02). The 5-year overall survival (OS) for HM patients was 33% with a median OS of 45.0 months; while 5-year OS was 23% and median OS was 32.3 months for PM patients (p=0.02). In a proportional hazards regression model, performance status and pre-operative chemotherapy had no significant effect on survival, while increased age (p=0.02) and PM (p=0.03) were associated with decreased OS. Postoperative morbidity was 38% versus 51% (p=0.04) and mortality was 3.0% versus 2.3% (p=0.73) in the HM and PM groups, respectively. Conclusions: Disease-free survival and OS are worse for patients who received complete cytoreduction and CS/HIPEC for PM compared to margin-negative liver resection for HM suggesting a more aggressive tumor biology in PM.



Kaplan-Meier curve for overall survival of metastatic colorectal cancer patients after surgical resection for liver and peritoneal metastases

P164

Unplanned Admissions and Outpatient Visits of Patients with Colorectal Peritoneal Carcinomatosis V.G. Gava,[1]* P.B. Paty,[2] A. Cercek,[2] M.R. Weiser,[2] L.K. Temple,[2] J.G. Guillem,[2] L. Saltz,[2] G.M. Nash.[2]
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Introduction: The morbidity of colorectal (CRC) peritoneal carcinomatosis (PC) is poorly described. We describe the need for unplanned admissions, outpatient visits, and interventions for patients with CRC and PC. Methods: A retrospective, single center experience (1998-2007) in the management of patients with CRC and PC as the unique site of metastatic disease. Results: A total of 214 patients were identified. The median age and Charlson Score were respectively 56 and 9.5 (8-17). Synchronous PC was present in 123 (58%) and the diagnosis was made by imaging in 103 (48%) patients. ECOG 0-1 was observed in 173 (95%). The initial approach was systemic chemotherapy (CH) for 162 (75%) patients and elective surgery for 52 patients. The median survival and the follow-up at the institution were 21 and 15 months, respectively. A total of 368 urgent admissions (2661 hospital days) and 142 procedures were performed on the 107 (50%) patients. The median interval between the diagnosis of PC and first hospitalization was 10.2 months (0 – 59). The median length of the first admission was 4 (1 – 59) days. Of those admitted, 70 (65%) underwent a procedure and 93 (87%) required more than one hospitalization. The median total admission length was 16 (1-137) days. After admission the median survival was 9.1 (5.4 – 12.9) months. Gastrointestinal (GI) symptoms related to abdominal disease were responsible for 221 admissions in 113 patients (56%). A total of 103 procedures were done in 72 (36%) patients. GI obstruction occurred in 75 patients (37%) and a palliative procedure was required by 68% of them. Median number of admissions for GI obstruction was 1 (1-8). Hospitalization to control abdominal pain was required by 31 (15%) of patients. There were 225 unplanned outpatient visits for 85 patients. Of those, 30 patients (35%) came for abdominal pain on at least on occasion. Paracentesis was required for 9 patients. Conclusion: Peritoneal disease plays a major role in the morbidity of PC from CRC. The majority of patients required unplanned admission, and a majority of those had invasive procedures, to palliate their abdominal symptoms.

P165

Distant Recurrence is the Main Problem in Modern Multidisciplinary Rectal Cancer Treatment, Not Local Recurrence
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Aim: The purpose of this multicenter cohort study was to evaluate whether a differentiated treatment of primary rectal cancer based on MRI can reduce the number of incomplete resections and local recurrences and improve recurrence-free and overall survival. Methods: From February 2003 until January 2008 296 patients with rectal cancer underwent preoperative MRI using a lymph node specific contrast agent to predict CRM, T- and N-stage. Based on expert reading of the MRI, patients were stratified in: (a) low risk for local recurrence (wide CRM and N0 status), (b) intermediate risk and (c) high risk (close/involved CRM, N2 status or distal tumours). Mainly based on this MRI risk assessment patients were treated with (a) surgery only (TME or local excision), (b) preoperative 5x5 Gy + TME, and (c) a long course of chemoradiation therapy followed by surgery after a 6-8 week interval. Results: Overall 228 patients underwent treatment with curative intent: 49 with surgery only, 86 with 5x5 Gy and surgery and 93 with chemoradiation and surgery. The number of complete resections (margin > 1mm) was 218 (95.6%). At a median follow-up of 41 months the 3- year local recurrence rate, disease-free survival rate and overall survival rate is 2.2%, 80% and 84.5% respectively. Conclusion: With a differentiated multimodality treatment based on dedicated preoperative MR imaging, local recurrence is no longer the main problem in rectal cancer treatment. The new challenges are early diagnosis, treatment and preferably prevention of metastatic disease.

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Influence of Perfusion Temperature during Oxaliplatin-based Hyperthermic Intraperitoneal Chemoperfusion (HIPEC) on Postoperative Outcome W.P. Ceelen,* Y. Van Nieuwenhove, P. Pattyn.
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Introduction Cytoreduction combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) is increasingly used in peritoneal surface cancer patients. The procedure does carry a significant postoperative morbidity. It is unknown, to what extent peritoneal perfusion temperature affects postoperative outcome. Methods Patients with carcinomatosis from colorectal or ovarian cancer underwent cytoreduction and HIPEC using oxaliplatin (460 mg/m2 in D5%, open abdomen) during 30 minutes at 39°-41°C. Intraperitoneal (IP) temperature was measured at three locations using thermocouple probes. The area under the temperature versus time curve (AUCt) and maximal temperature (Tmax) were calculated and their influence on postoperative morbidity was assessed statistically. Data are presented using mean±SD. Results From July 2005 until February 2011, 138 patients (56% female, mean age 59 years) were treated. Operating time was 9.6 ± 2.8 hours; Tmax was 40.5 ± 1.1°C while AUCt was 1340.6 ± 91.6 °C*min. Postoperative mortality was 1.4% while major morbidity and reoperation rate were 27.5% and 18% respectively. In patients with at least one bowel anastomosis (64.5%), leakage occurred in 18%. Median hospital stay was 18 days. Anastomotic leakage was affected by the number of anastomosis (1.7±0.97 versus 2±0.63 in patients without and with leakage respectively; P=0.039) but not by Tmax, AUCt, age, gender, operating time, or BMI in univariate analysis. Overall complications were not affected by Tmax or AUCt, but Tmax corrlated with postoperative elevation of gamma-GT. Conclusions Cytoreduction and HIPEC using high dose oxaliplatin carry an increased risk of anastomotic leakage. Neither Tmax not AUCt affect the risk of anastomotic leakage or overall major comlication rate. Therefore, efforts should be directed towards developing safer IP chemotherapy regimens rather than abandoning the hyperthermia component.

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Simultaneous Liver and Colorectal Resections for Synchronous Cancers Show Similar Longterm Outcome as Staged Procedures

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Background: Twenty-five percent of patients with colorectal cancer will present with synchronous liver metastasis. Due to improvements in surgical and perioperative management, simultaneous liver and colon resection is an accepted procedure. Patients and Methods: Patients with colorectal cancer with synchronous liver disease who were candidates for complete resection were identified from departmental databases. In patients submitted to staged resections, only patients who underwent both resections at our institution were included. The focus of analysis was set on oncologic outcome based on tumor characteristics and type of resection (staged versus simultaneous). Results: Between 1984 and 2008, 429 patients underwent both surgical procedures for stage IV colorectal cancer at our institution. 320 (74.6%) of these patients had simultaneous resection, and 109 had staged resection. There were no differences in age or gender between the groups. The median follow up time was 37 months. Neither disease-free nor overall survival rates differed significantly between the two treatment strategies (p=0.09 and 0.52). The extent of the liver procedure (more than 3 segments) was defined as a significant factor in disease-free and overall survival (both p<0.01). Other results of the multivariable analysis are provided in Figure 1. Conclusion: Simultaneous liver and colorectal resection for synchronous metastatic disease is associated with long term outcome that is similar to staged procedures.

Figure 1

	overall survival	disease free survival
Staged procedure	ns	ns
location of primary tumor	ns	ns
liver procedure (major)	p<0.01	p=0.01
Fong score	p<0.01	p<0.01
age	p<0.01	ns

P168

Prevalence of Genetic Polymorphisms Varies by Race/Ethnicity among Colon Cancer Patients in Los Angeles County

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BACKGROUND: Though disparate outcomes in colon cancer may be multifactorial, racial/ethnic disparities persist despite adjusting for these factors. Genetic alterations, including single-nucleotide polymorphisms (SNPs), have been shown to predict treatment response in colorectal cancer. Here, we evaluate the variability of genetic alterations in colon cancer patients by examining SNPs in the major racial/ethnic groups. METHODS: We obtained 76 normal tissue specimens from colon cancer patients of different race and ethnicity treated at our institution. DNA was extracted and analyzed for 6 SNPs (MTHFR 677C>T, XRCC1 685C>T, XRCC1 1301G>A, XPD 2282A>C, TP53 215G>C, and CCND1 870G>A) by polymerase chain reaction and direct sequencing. Prevalence of each allelic combination was compared between groups by the chi-square test. RESULTS: Archived colon cancer tissues were obtained from whites, blacks, Hispanics and Asians (n=19 per group). From tissue genotyping, we identified statistically significant differences in prevalence of CCND1 870G>A between groups (p=0.0428). Specifically, whites and Asians had significantly higher prevalence of CCND1 870G>A than blacks and Hispanics (100% and 94%, vs. 68% and 79%, respectively). Furthermore, whites and Asians were more frequently heterozygous (G/A) for the SNP (89% in both), whereas Hispanics comprised the largest proportion (16%) of patients homozygous for CCND1 870G>A. Overall, the allelic frequency of CCND1 870G>A varied among the 4 racial/ethnic groups. Other SNPs in treatment-related pathways were evaluated, but there was no difference in prevalence of the other 5 SNPs (MTHFR 677C>T, XRCC1 685C>T, XRCC1 1301G>A, XPD 2282A>C and TP53 215G>C) between the groups (Table 1). CONCLUSION: Our findings demonstrate that detection of specific genetic polymorphisms differs between the major racial/ethnic groups with colon cancer. Differences in the prevalence of CCND1 870G>A, which affects cell-cycle progression, suggests a potential mechanism for disparities in cancer susceptibility and progression. Therefore, identification of such genetic variability may support a genetic basis for racial disparities in cancer outcomes.

Gene polymorphism		RACE/ETHNICITY				Total	*P*-value
		Whites	Blacks	Hispanics	Asians		
CCND1 870G>A (rs603965)	G/G	0%	32%	21%	5%	11	0.0428
	G/A	89%	68%	63%	89%	59	
	A/A	11%	0%	16%	5%	0	
XRCC1 1301G>A (rs25487)	G/G	32%	42%	37%	47%	30	0.7767
	G/A	68%	58%	63%	53%	46	
	A/A	0%	0%	0%	0%	0	
XRCC1 685C>T (rs1799782)	C/C	100%	100%	95%	89%	73	0.2819
	C/T	0%	0%	5%	11%	3	
	T/T	0%	0%	0%	0%	0	
XPD 2282A>C (rs13181)	A/A	42%	47%	58%	89%	45	0.0713
	A/C	47%	47%	32%	11%	26	
	C/C	11%	5%	11%	0%	0	
MTHFR 677C>T (rs1801133)	C/C	42%	74%	47%	53%	41	0.3815
	C/T	42%	26%	32%	32%	25	
	T/T	16%	0%	21%	16%	10	
TP53 215G>C (rs1042522)	G/G	53%	26%	53%	42%	33	0.5462
	G/C	32%	42%	37%	42%	29	
	C/C	16%	32%	11%	16%	14	

P169

Lateral Node Dissection In Locally Advanced Rectal Cancer with Radiologically Detected Extramesorectal Node Metastasis

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Rationale The incidence of lateral node metastasis in rectal cancer ranges from 10-23%.Patients with lateral node deposits show poor outcome, yet lateral node dissection may provide a favorable prognostic value with respect to local disease control. Aim The purpose of the study is to evaluate the clinical outcome of patients that underwent lateral node dissection for radiologically detected extramesorectal nodes. Methods This study ran from 2005 through 2010 and involved 75 patients with stage II and III rectal cancer who received neoadjuvant long course chemo radiation followed by total mesorectal excision and concomitant lateral node dissection for radiologically diagnosed extramesorectal nodal metastasis.MRI and multidetector CT were used to assess primary tumour stage, lateral, mesorectal and paraaortic lymph nodes.Lymph node larger than 0.5cm at the short –axis diameter,with speculated edges or heterogenic pattern was considered malignant. PET/CT was used in uncertain diagnosis. Results The perioperative mortality occurred in 3% and surgical morbidity in 16%.The positive predictive value (PPV) for the radiollogically diagnosed extramesorectal nodal metastasis was 97% for lateral nodes and 69.6% for the mesenteric nodes. Pathological examination revealed positive lateral, mesenteric,lateral &mesenteric nodes (42.6%-37.3%-12.3%) respectively. The 5-year cancer specific survival rate in patients with lateral,mesenteric, lateral&mesenteric nodes was (41.3%-60%-23.2%). The 5- year disease free survival in patients with the same groups was (32%-45%-21%). Conclusion The prognostic significance, the associated morbidity and the false positive results of radiological diagnosis of lateral nodal disease should decide the role of lateral node dissection in rectal cancer.

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Evaluation of the Prognostic Value of Guanylyl Cyclase C (GCC) Lymph Node (LN) Classification in Patients with Stage II Colon Cancer: A Pooled Analysis

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BACKGROUND: Identification of a sensitive and specific prognostic marker would aid in the management of patients (pts) with standard histopathology node negative colon cancer (CC). We conducted a pooled individual pt data analysis to confirm the prognostic value of GCC for disease recurrence in untreated stage II CC. METHODS: GCC mRNA was quantified by RT-qPCR using formalin-fixed LN from 310 stage II pts diagnosed from 1991 – 2006 enrolled in two studies (Sargent2011[study1] & Haince2009[study2]). Patients

were classified by GCC LN ratio (LNR) (high risk: LNR ≥ 0.1; low risk: LNR < 0.1), with LNR defined as number of GCC positive LN divided by number of informative LNs. Clinical outcomes included time to recurrence (TTR), overall survival (OS), disease-specific survival (DFS) and disease-free survival (PFS). Stratified log-rank tests and multivariate Cox models assessed the association between clinical outcomes and GCC LN status. RESULTS: Study 1 (n=241) and 2 (n=69) were similar in gender (42% males vs. 41%, p=0.80) and T stage (95% T3 vs. 99%, p=0.20), but study 1 pts were slightly older (median age 74 vs. 68 years, p=0.02), with fewer grade 1 pts (8% vs. 24%, p=0.002) and a lower presence of lymphovascular invasion (10% vs. 30%, p=<.001). The 5-year recurrence rates were 15.8% and 24.9% in study 1 and 2 respectively. Overall, pts classified as GCC LNR high risk had significantly higher risk of event for TTR, OS, DSS and DFS. These outcome differences remained after adjusting for age at surgery, T stage, grade, number of LNs examined, and presence of lymphovascular invasion (Table). In a secondary analysis with low risk stage II patients (T3, ≥12 LNs examined, and negative surgical margins; n=241), a strong relationship between GCC LNR and recurrence risk was also observed (TTR HR=4.34, 95% CI=2.07 – 9.13, p<.001). CONCLUSIONS: Pts with GCC LNR high risk status have significantly poorer outcomes compared to pts with low risk status, particularly among those traditionally considered to be low risk.

Hazard Ratios Comparing High Risk (LNR ≥ 0.1) and Low Risk (LNR < 0.1) Groups

Outcomes	LNR risk group	3-year event-free rates [95% CI]	Univariate		Multivariate	
			HR [95% CI]	P	HR [95% CI]	P
TTR	High	0.81 [0.74, 0.90]	2.99 [1.65, 5.42]	<.001	2.55 [1.41, 4.61]	0.002
	Low	0.91 [0.87, 0.95]				
OS	High	0.85 [0.79, 0.92]	1.83 [1.17, 2.87]	0.008	1.72 [1.06, 2.80]	0.028
	Low	0.92 [0.88, 0.96]				
DSS	High	0.81 [0.74, 0.90]	3.07 [1.73, 5.48]	<.001	2.62 [1.47, 4.67]	0.001
	Low	0.91 [0.87, 0.95]				
DFS	High	0.75 [0.67, 0.84]	2.23 [1.51, 3.31]	<.001	2.15 [1.42, 3.25]	<.001
	Low	0.86 [0.82, 0.91]				

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Impact of Lymph Node Metastasis on Survival Outcome for Patients Diagnosed with Mucinous Carcinoma of the Appendix: The Role of Right Hemicolectomy C.U. Ihemelandu,* G. Russell, P. Shen, J.H. Stewart, K. Votanopoulos, E.A. Levine. *General Surgery, Section of Surgical Oncology, Wake Forest School of Medicine, Winston-Salem, NC.*

Background:- The optimal management strategy for an incidentally diagnosed mucinous adenocarcinoma of the appendix following an appendectomy remains controversial. Our aim is to evaluate and validate the prognostic significance of lymph node metastasis and as such a right hemicolectomy in this cohort of patients. Methods: - Retrospective analysis of a prospectively collected database for all patients with assessable data treated for an appendiceal mucinous carcinoma peritonei from 1993-2011 (n= 394). Results: - 285(72.3%) patients were diagnosed with low grade mucinous carcinoma peritonei (MCP) vs. 109(27.7%) with high grade MCP. 148(59%) underwent a right hemicolectomy vs. 103(41%) who underwent an appendectomy. 66(26.8%) had positive lymph nodes vs. 180(73.2%) with negative lymph nodes. Overall median survival was 61 months, a significant difference in survival was noted between low and high grade MCP 85 vs. 18 months respectively (p=0.000). Survival time for patients with no lymph node metastasis was 82 vs. 17 months for those with nodal metastasis(p=0.000). Tumor grade was a significant predictor of lymph node metastasis 11(95% CI 5.7 – 23, p=0.000). There was a significant correlation between undergoing a right hemicolectomy and having a high grade MCP and lymph node metastasis (spearman correlation p=0.000). The rate of nodal positivity amongst patients with low grade tumor in our study population was 8.5%. Independent predictors for survival outcome in multivariate analysis included; ECOG performance status, peritoneal carcinomatosis index, tumor grade, and surgical therapy, with patients undergoing a right hemicolectomy 9 times more likely to have a shorter survival time (95% CI 1.6 – 34.9 p=0.01). Nodal status failed to achieve statistical significance in multivariate analysis. Conclusion: - Tumor grade was a significant predictor of nodal metastasis, and therefore may help identify patients most likely to benefit from a hemicolectomy. For patients with a low grade MCP a right hemicolectomy does not seem to afford any survival benefits.

Clinicopathologic Characteristics for Patients treated with an Appendectomy vs. a Right hemicolectomy

Characteristics	Appendectomy (N = 103)	Right hemicolectomy (N = 148)	P value
Nodal Status -Negative -Positive	54(100%) 0(0.0%)	57(57.6%) 42(42.4%)	0.000
Histologic grade -Low grade -High grade	84(88.4%) 11(11.6%)	75(55.6%) 60(44.4%)	0.000
Median Survival (mths) 0verall	152(29.5)	30(3.5)	0.000
Median Survival(mths) -Low grade - High grade	192(0.0) 19(8.4)	77(13.1) 16(2.4)	0.01

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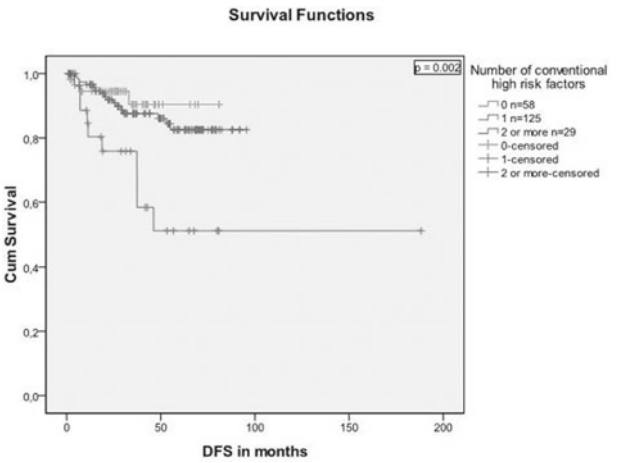
The Number of High Risk Factors is Related to Outcome in Stage II Colon Cancer Patients B. Koebrugge,[1]* D.J. Lips,[2] J.F. Vogelaar,[2] H.F. Pruijt,[2] H.C. Van der Linden,[2] M.F. Ernst,[2] K. Bosscha.[2] *1. surgery, Leiden University Medical Center, Leiden, Netherlands; 2. Jeroen Bosch Hospital, 's Hertogenbosch, Netherlands.*

Introduction: A subgroup of stage II colonic cancer patients are considered to be at high-risk for recurrent/metastatic disease based on 1) tumor obstruction/perforation 2) < 10 lymph nodes 3) T4 lesions and 4) lymphangio-invasion. Their prognosis is regarded as comparable to stage III (T1-4N+M0) colonic cancer and it is therefore strongly advised to treat them with adjuvant chemotherapy. The purpose of this study was i) to determine the magnitude of prognostic significance of the conventional high-risk factors and ii) to determine whether the number of high-risk factors influences outcome. Methods: We retrospectively analyzed 212 stage II colonic cancer patients undergoing surgery between January 2002 and December 2008. No adjuvant chemotherapy was given. Survival analyses were performed. Results: 154/212(73%) patients were considered to be high-risk patients based on conventional high-risk factors. 58 patients did not meet any high-risk factor, 125 patients met 1 high-risk factor and 29 patients met >2 high-risk factors. Median follow up was 40 months. Multivariate analysis identified four independent risk factors for recurrent/metastatic disease: age, obstruction, perforation and lymphangio-invasion. The three-year-DFS-rates for the low-risk group, the high-risk group with 1 high-risk-factor and the high-risk group with ≥ 2 high-risk-criteria are 90.4%, 87.6% and 75.9% respectively. Patients meeting >2 conventional high-risk criteria had a significantly worse three-year-disease free survival (p < 0.002). Conclusions: Four independent high-risk factors were identified. The number of high-risk factors does influence outcome. More attention should be given to the definition and treatment of high-risk stage II colonic cancer patients.



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Cytoreduction and Heated Intraperitoneal Chemotherapy: Diverting Ileostomy not Always Necessary? Y.J. McConnell,* V. Dong, T. Ho, W. Temple, L.A. Mack. *Division of Surgical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada.*

Background: Cytoreductive surgery with heated intraperitoneal chemotherapy (CS+HIPEC) is used to treat peritoneal carcinomatosis. CS+HIPEC has significant associated gastrointestinal (GI) morbidity, including anastomotic leak, abscess, and fistula. Many centres use routine diverting ileostomy to avert clinically significant GI complications, although data to support this practice are lacking. Here the rate of GI morbidity is reviewed at our centre, where diverting ileostomy is infrequently used. Methods: The prospectively maintained database of CS+HIPEC patients at the University of Calgary was reviewed for a recent consecutive cohort. Abstracted data included patient, tumor, and technical factors, as well as in-hospital/30-day complications. Univariate and multivariate analyses were used to analyse associations between the rate of Grade III/IV GI-related complications, diverting ileostomy creation, peritoneal carcinomatosis index (PCI), cytoreduction score (CCR), and other clinicodemographic and technical factors. Results: Between April 2006 and October 2010, 102 patients underwent CS+HIPEC. The PCI was >26 in 40 patients (39.5%) and cytoreduction to no visible disease (CCR0) was achieved in 92 patients (90.2%). Left-sided colonic or rectal anastomoses were formed in 22 patients (21.6%). End ileostomy or colostomy was formed in 35 patients (34.3%). Only 3 patients (2.9%) had creation of a diverting ileostomy. Grade III/IV GI-related complications occurred in 26 patients (25.5%) which is comparable to literature values of 22-30%. Grade III/IV GI-related complications were more common amongst patients with a PCI >26 (p=0.07) and those in which cytoreduction to <2.5-mm tumor nodules (CCR1) was achieved (p=0.02). Conclusion: In a prospective cohort of patients undergoing CS+HIPEC, including many with high PCI values, a very low rate of diverting ileostomy creation was not associated with an increased rate of major GI-related complications compared to centres where diverting ileostomy is used more routinely. The main factor in the development of GI-related complications appears to be the extent of surgical intervention, as reflected by PCI and CCR scores.

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Port Site Metastases in Patients with Stage IV Appendiceal Neoplasm H.M. El Halabi,* C. Wosu, R. MacDonald, J. Francis, S. Shankar, C. Nieroda, P. Ledakis, V. Gushchin, A. Sardi. *Institute for cancer care Mercy Medical center, Baltimore, MD.*

Introduction: Port site metastases have been reported after laparoscopy in gastrointestinal, hepato-biliary and gynecological tumors. The incidence of port site metastases in carcinomatosis from appendiceal neoplasm has not been reported. This study evaluated the incidence and significance of port site metastases in patients with appendiceal neoplasm that underwent cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC). Methods: A retrospective analysis of a prospective database was conducted. Patients with appendiceal neoplasm that had laparoscopy prior to CRS/HIPEC were studied. All port sites were excised at CRS/HIPEC. Patients who had port site metastases were compared to those who did not. Overall survival (OS) was estimated by plotting Kaplan-Meier survival curves and differences were tested by using the log-rank test. Results: From 169 patients with carcinomatosis from appendiceal primary that had CRS/HIPEC, 38 had prior laparoscopy. 13/38 patients (34%) had port site metastases and 25 did not. The characteristics of each group are summarized in the table below. At a mean follow up of 25 months (range 1-69 months), the 5-year OS for the port site metastases group and no port site involvement were 32% and 89 % (p=0.049), respectively. Conclusion: Port sites should be excised during CRS/HIPEC for carcinomatosis from appendiceal primary since port site metastasis is common and complete cytoreduction is essential for long term survival. In this study, presence of port site metastasis was associated with decreased OS and did portend a worse prognosis and more aggressive biology; these findings will need to be validated in studies with larger number of patients.

Port site metastases	N(%)	Mean age	M/F	PCI>20	PSS(2/3)	LN+	CC(0/1)	PMCA/DPAM
Yes	13(34%)	53	7/6	10(77%)	2(15%)	7(54%)	10(77%)	9/4
No	25(66%)	53	9/16	16(64%)	3(12%)	3(12%)	24(96%)	12/13
p value		0.9	0.3	0.5	0.7	0.01	0.1	0.3

Number (N), male/female (M/F), peritoneal cancer index (PCI), prior surgery score 2 or 3 (PSS 2/3), lymph node metastases (LN+), complete cytoreduction (CC 0/1), peritoneal mucinous carcinomatosis (PMCA), disseminated peritoneal adenomucinosis (DPAM).

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The Role of Lymphadenectomy in the Surgical Management of Anorectal Melanoma D. Perez,[1]* J. Shia,[2] A. Trakarnsanga,[1] L. Temple,[1] G. Nash,[1] R.D. Carvajal,[3] J. Guillem,[1] C. Ariyan,[1] M.R. Weiser.[1] *1. Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; 2. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; 3. Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY.*

Objectives: 1) Analyze the role of lymphadenectomy on local control and survival. 2) Assess the pattern of treatment failure. 3) Identify prognostic parameters. Background: The impact of lymph node metastases on local tumor control and distant failure in patients with anal melanoma has not been fully studied. Understanding the significance of lymphatic dissemination might assist with the stratification of patients to organ preservation or radical surgery. Methods: A retrospective review was performed of all patients with anorectal melanoma who underwent surgery at our institution between 1985 and 2010. Abdominoperineal resection (APR) was performed in 27 (40%) cases and wide local excision (WLE) in 41 (60%). The extent of primary surgery and locoregional lymphadenectomy (mesorectal, inguinal), the patterns of treatment failure and pathological parameters were analyzed. The progression-free survival (PFS) and disease-specific survival (DSS) were analyzed with the Kaplan-Meier product limit method. Results: In those patients undergoing rectal resection, DSS was not associated with the presence (69%) or absence (31%) of metastatic melanoma in mesorectal lymph nodes. There was a trend toward improved DSS in patients with clinically negative inguinal nodes (n=24) compared with those having inguinal metastasis (n=10, p=0.09). The extent of surgery (WLE vs. APR) was not associated with the subsequent development of distant disease. However, local recurrence was more common after WLE but was also associated with distant disease (P=0.04). Perineural invasion was significantly correlated with PFS (P=0.002) and poor DSS (P=0.001). Conclusion: Outcome following resection of anorectal melanoma is independent of locoregional lymph node metastasis and lymphadenectomy should be reserved for symptomatic disease. Perineural invasion is a powerful prognostic marker and should be further explored in clinical trials.

Prognostic role of locoregional lymph node metastasis on disease progression and survival

LN status	No	PFS	P*	DSS	P*
Mesorectum					
Positive	8	14 (5-31)	0.62	30 (10-139)	0.71
Negative	18	12 (8-76)		27 (10-51)	
Inguinal					
Positive	10	8 (2-13)	0.65	21 (8-34)	0.09
Negative	24	11 (2-75)		28 (13-137)	

LN: lymph node, No: Number of patients available for analysis, PFS: Progression-free survival (months), DSS: Disease-specific survival (months). *Kaplan-Meier product limit method. Values are shown as median and corresponding interquartile range.

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Association between Delays in Adjuvant Chemotherapy for Stage II and III Colon Cancer and Increased Mortality A.B. Haynes,* Y. Chiang, B.W. Feig, Y. Xing, G.J. Chang, Y. You, J.N. Cormier. *Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction Administration of adjuvant chemotherapy is the standard of care for stage III and high risk stage II adenocarcinoma of the colon. There are conflicting data regarding the optimum interval for the initiation of adjuvant therapy and whether this affects survival. Methods Patients were identified from the National Cancer Database (1998-2002) who received adjuvant chemotherapy after resection of stage II or III colon cancer. Multivariate analyses were performed to examine the associations between various time intervals from surgery to chemotherapy initiation and overall and relative survival. Relative survival was used as a surrogate for disease-specific survival and was calculated by the method of Dickman et al. Results 46,266 stage II or III colon cancer patients who received chemotherapy after definitive surgery were identified. The relationship between timing of adjuvant chemotherapy and survival is reported in Table 1. Delay of chemotherapy beyond 8 weeks postoperatively was associated with an increased likelihood of death (p<0.001) in a relative survival model, with a hazard ratio for death of 1.30 (95% CI: 1.08, 1.56) and

1.19 (95% CI: 1.11, 1.28) for stage II and III patients in the 8 to 12 week interval, respectively. Longer delays (≥ 16 weeks) were associated with worse outcomes, with as much as a 14% and 7.6% absolute decrease in relative survival for stage II and III, respectively. Other independent factors associated with reduced survival included gender, race, type of insurance, margin status, and tumor grade. Conclusions Delay in the initiation of adjuvant chemotherapy beyond eight weeks is an independent predictor of increased mortality. While other factors contribute to the risk of death from disease, chemotherapy delays may potentially be preventable. Policy interventions should be developed to encourage the administration of chemotherapy within eight weeks of resection for stage II and III colon cancer when indicated. Further effort should be expended to understand the etiology of and mitigate these delays.

Relationship Between Time to Chemotherapy and Survival

		Time From Surgery to Initiation of Adjuvant Chemotherapy				
Stage II (n=13,939)		<4 Weeks (n=2,953)	4-8 Weeks (n=7,712)	8-12 Weeks (n=2,098)	12-16 Weeks (n=703)	≥16 Weeks (n=473)
	5-year Relative Survival (%)	89.9	91.1	88.0	82.8	77.1
	HR (95% CI) for Relative Survival	1.21 (1.02,1.44)	Reference	1.30 (1.08,1.56)	1.72 (1.34,2.21)	2.07 (1.57,2.72)
	5-year Overall Survival (%)	80.4	81.8	78.1	74.1	68.5
	HR (95% CI) for Overall Survival	1.08 (0.98,1.19)	Reference	1.17 (1.05,1.29)	1.41 (1.22,1.64)	1.70 (1.43,2.01)
Stage III (n=32,327)						
	5-year Relative Survival (%)	69.4	71.6	66.7	65.1	64.0
	HR (95% CI) for Relative Survival	1.07 (1.02,1.14)	Reference	1.19 (1.11,1.28)	1.24 (1.11, 1.39)	1.27 (1.11,1.45)
	5-year Overall Survival (%)	61.4	63.2	57.4	56.6	55.9
	HR (95% CI) for Overall Survival	1.05 (1.01,1.10)	Reference	1.15 (1.09, 1.21)	1.21 (1.12,1.32)	1.23 (1.11,1.36)

All time intervals are inclusive of the lower boundary and exclusive of upper boundary. Relative survival is calculated using population tables after the method of Dickman, et al.

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WITHDRAWN

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Increased Risk of Neoplasm Associated with Interval Appendectomy
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Background: The role of interval appendectomy after conservative management of perforated appendicitis remains controversial. Determining the etiology of perforated appendicitis is one reason to perform interval appendectomies. This study hypothesizes that there is an increased rate of neoplasm in patients undergoing interval appendectomy. Methods: This is a retrospective review of all patients over 18 years of age who underwent appendectomy for presumed appendicitis from January, 2006 to December, 2010 at a single, tertiary care institution. Demographic data, pathologic diagnosis, clinico-pathologic characteristics, interval resection rate, and complication data were collected and analyzed. Results: During the study period, 376 patients underwent appendectomy. The mean age was 41 years (range 18 to 94). Interval appendectomy was performed in 18 patients (5.0%) (age 28 to 74). Neoplasms were identified in 14 patients (3.7 %); 6 were found in patients who had undergone interval appendectomy (33%). Nine were mucinous tumors (69.2%), 5 of which were associated with interval appendectomies. Neoplasms were identified in 8.3% of patients between 35 and 55 years old. Conclusions: Mucinous neoplasms of the appendix were found in 33% of patients undergoing interval appendectomy. Interval appendectomies should be considered in all patients 35 years and older due to increased risk of appendiceal neoplasm

Table 1: Incidence of Appendiceal Neoplasm by Age

Age	Number of Patients	Mucinous Neoplasms	Carcinoid Tumors	Other Tumors
18-35	163	0	0	0
35-39	39	2 (5.13 %)	0	0
40-44	41	1 (2.4 %)*	1 (2.4 %)	1 (2.4%)
45-49	27	2 (7.4 %)*	0	1 (3.7 %)
50-54	25	2 (8.0 %) **	1 (4.0 %)	0
55-59	20	0	0	1 (5.0%)*
60-64	23	0	0	0
65-69	14	1 (7.1 %)	0	0
70-74	10	1 (10.0 %)*	0	0
>75	14	0	0	0

*Interval appendectomy

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Adherence to NCCN Guidelines is Associated with Improved Survival in High Risk Stage II and Stage III Colon Cancer
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Introduction: Evidence-based treatment guidelines have been proposed as a potential quality metric for cancer care. Significant variability in the treatment of high-risk stage II (defined by tumor depth, histologic grade, margin status, and number of nodes retrieved) and stage III colon cancer patients has been noted in the National Cancer Database (NCDB). The current study examines whether adherence to guidelines is associated with improved survival. Methods: Patients with colon adenocarcinoma (1998-2002) were identified from the NCDB. The stage-specific National Comprehensive Cancer Network (NCCN) guidelines were used to classify patients into two groups based on whether they were treated in accordance to guidelines (adherent or non-adherent). Overall survival (OS) and relative survival (RS) were calculated for both groups. Relative survival was used as a surrogate for disease-specific survival and calculated using the methods of Dickman et al. Results: A total of 77,350 patients were included in the analytic cohort. Stage-specific outcomes were compared and clearly stage is an independent predictor of survival. As reported in our previous analyses, nonadherence as a result of omission of chemotherapy, was noted in 64.3% and 26.4% of high-risk stage II and stage III patients, respectively. Nonadherence was associated with decreased OS and RS with a hazard ratio of 1.43 (95% CI: 1.33, 1.54) for high-risk stage II and 1.89 (95% CI: 1.82, 1.95) for stage III ($p < 0.001$, Table 1) RS. In addition, regression analysis demonstrated that gender, age, race, insurance, income, and type of facility were also associated with differences in RS. Conclusions: Guideline-based practice, particularly for high-risk stage II and stage III colon cancer, is associated with improved survival outcomes. Therefore, these guidelines may be appropriate as a metric of performance that is comparable across various institutions. Additionally, factors associated with deviations from guidelines can be used to focus improvements in the access to and delivery of cancer treatment.

Survival outcomes based on adherence to NCCN guidelines

	Non-adherent	Adherent
High Risk Stage II (n=28592)		
5-yr Overall Survival	66.5	76.8
5-yr Relative Survival	77.5	84.9
RS Hazard Ratio (95% CI)	1.43 (1.33-1.54)	Referent
Stage III (n=48758)		
5-yr Overall Survival	44.4	62.2
5-yr Relative Survival	51	69.1
RS Hazard Ratio (95% CI)	1.89 (1.82-1.95)	Referent

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Cytoreductive Surgery (CS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Elderly K.I. Votanopoulos,* P. Shen, J.H. Stewart, G. Russell, E.A. Levine, N.A. Newman. *Surgical Oncology, Wake Forest University, Winston Salem, NC.*

Background: CS-HIPEC is the treatment most likely to achieve prolonged survival in peritoneal carcinomatosis. Yet, in elderly patients is controversial due to associated morbidity. Therefore, we chose to review our experience in patients older than 70 years of age. Methods: A retrospective analysis of a prospective database of 950 procedures was performed. Type of malignancy,

ECOG, resection status, hospital and ICU stay, comorbidities, morbidity, mortality and survival were reviewed. Results: 81 patients (median age 73, range 70-87) underwent CS-HIPEC between 1991-2011, including 32 patients with appendiceal primaries, 20 colon cancers, 10 mesotheliomas, 8 ovarian, 6 gastric cancers and 5 others. Median follow up was 48.1 months. Functional status was graded as 0/1 for 77% of the patients; R0/1 resection was achieved in 44%. Median survival was 31.8 months for appendiceal cancer, 41.5 for mesothelioma, 54 for ovarian cancer, 13.2 for colon cancer and 7.6 for gastric cancer. The 30 day mortality was 13.9%. The combined major and minor morbidity was 55.6%. Median ICU and hospital stay for uncomplicated patients was 1 and 8 days respectively. The 3 month mortality was 27.4%. There were no deaths in the octogenarian group. In multivariate analysis, age, EGOG and R status of resection (p=0.051) were not statistically significant. The type of primary (p=0.03), albumin (p=0.02 HR=0.60) and year that the procedure was performed (p=0.006 HR=0.93) were predictive of survival. The risk of death was reduced by 40% for each additional gram of albumin and 7% for each annual increment in the institution's experience. There was a significant drop in 1 and 3 month mortality over time to 10% and 19% respectively while the median survival increased from 11.2 months (N=39) to 46.9 months (N=42). Conclusions: CS-HIPEC in the elderly is associated with a steep learning curve and considerable morbidity and mortality. However, age alone is not a contraindication for the procedure. Tertiary centers with experience in the treatment of peritoneal surface disease and careful patient selection are key factors for prolonged survival.

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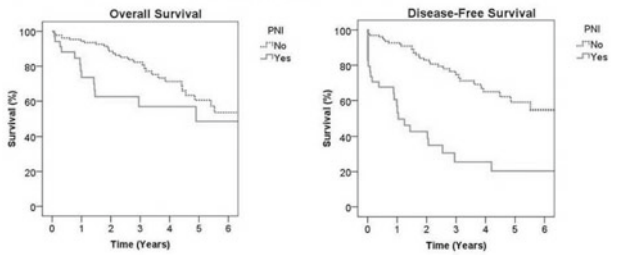
Perineural Invasion is Associated with Poor Outcomes in Rectal Cancer S.T. Orcutt,* L.T. Li, D.A. Anaya, A. Artinyan, S.S. Awad, D.H. Berger, D. Albo. *Baylor College of Medicine, Department of Surgery, Division of Surgical Oncology, Houston, TX.*

Introduction: We have previously reported that perineural invasion (PNI) is associated with poor outcomes in colorectal cancer. Currently the role of PNI for determining the prognosis in the subset of patients with rectal cancer is uncertain. We hypothesize that PNI in rectal cancer patients would be associated with decreased long-term survival and would be an independent predictor of poor outcomes. Methods: 176 patients undergoing rectal cancer resections were identified from a comprehensive database of all patients who had colorectal cancer surgery at our institution from 2002-2011. This database includes information on patient and tumor characteristics, as well as long-term follow-up. Patients were placed into groups based on the presence or absence of PNI. Survival analyses were performed using the Kaplan-Meier method, with log-rank test for comparison. Cox regression was performed to identify predictors of decreased survival. Results: PNI was identified in 34 (19.3%) patients. PNI positivity increased with higher stage, with 0% of Stage 1 patients, 17% of Stage 2 patients, 22% of Stage 3 patients, and 73% of Stage 4 patients having PNI (p<0.0005). Gross or microscopic positive margins at resection were associated with higher rates of PNI as well (80% of R1 or R2 resections vs. 18% of R0 resections, p=0.006). Local recurrence rates were three-fold higher in the PNI positive group than in the PNI negative group, although not statistically significant (6% vs. 2%, p=0.271). 5-year overall and disease-free survival were worse in the PNI positive group than in the PNI negative group (49% vs. 61%, p=0.055 and 20% vs. 59%, p<0.0005, see Figure 1). On Cox regression analysis of disease-free survival, correcting for age, race, stage, margin positivity, and tumor grade, PNI was the only independent predictor of decreased survival (HR 2.26 [1.13-4.53], p=0.022). Conclusions: Perineural invasion is an important tumor characteristic having a poor prognostic effect in patients with rectal cancer, primarily on disease-free survival. It should be taken into consideration when stratifying patients for aggressive therapies.

Figure 1. Perineural invasion (PNI) is associated with decreased 5-year overall and disease-free survival (p=0.055 and p<0.00005) in patients with rectal cancer.



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Deep Sequencing using Formalin Fixed Paraffin Embedded (FFPE) Rectal Cancer Biopsy Tissue Reveals a Novel miRNA Expression Profile in Patients with Rectal Cancer Z. Chen,[1]* H. Gao,[2] B. Mu,[2] J. Wang,[2] X. Wu,[2] H. Qin,[2] W. Li,[1] J. Garcia-Aguilar.[1] *1. Surgery, City of Hope, Duarte, CA; 2. City of Hope/ Beckman Research Institute, Duarte, CA.*

Background: miRNAs have been shown to be involved in tumor initiation, progression and metastasis in many cancers including colorectal cancer. However, miRNA profiling specifically in rectal cancer is not well characterized. Our objective was to generate a miRNA expression profile in locally advanced rectal cancer using formalin fixed paraffin embedded (FFPE) biopsy tissue collected from patients with locally advanced rectal cancer. Methods: We collected pre-treatment biopsy tissue and matched normal tissue from 40 rectal cancer patients treated with pre-operative chemoradiation (CRT) and total mesorectal excision (TME). We extracted 50-1000ng of total RNA from FFPE biopsies and optimized small RNA sample preparation for deep-sequencing. We then performed deep sequencing on biopsy and matched normal tissue and compared miRNA expression in biopsy and normal tissues using paired T-test and multiple testing (Q-bound <0.05) to determine significant miRNA expression changes in rectal cancer. Results: 182 miRNAs were differentially expressed in tumor versus normal tissues (Q-bound <0.05); 15 of these miRNAs showed a greater than 2-fold change in expression in tumor tissue; mir-18a, mir-135b, mir-503, mir-584, mir-106b, mir-224, mir-92a, mir-181d were up-regulated and mir-375, mir-378, mir-378c, mir-137, mir-378, mir-147b, mir-30a were down-regulated. miRNA mir-31 showed the highest up-regulation in tumor tissue (16-fold increase) while mir-215 expression decreased 8-fold in tumor compared to normal tissue. Tumor and normal tissues were completely separated by hierarchical cluster analysis based on their distinctive miRNA profiles. Conclusions: We optimized small RNA sample preparation for deep sequencing of miRNAs, an approach which may be useful for quantifying miRNA expression in tissues with limited starting material. We also identified a novel miRNA expression profile in rectal cancer that may be useful as a diagnostic biomarker of disease.

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Accuracy of MRI in Predicting Nodal Status after Neoadjuvant Chemoradiation for Rectal Cancer W.P. Ceelen,* P. De Munck, Y. Van Nieuwenhove, D. Vande Putte, N. Van Damme, T. Boterberg, P. Pattyn. *Ghent University Hospital, Ghent, Belgium.*

Introduction Organ sparing and 'wait and see' strategies are under evaluation in rectal cancer patients with an excellent clinical response to neoadjuvant chemoradiation (CRT). When considering such approaches, residual locoregional nodal metastasis should be excluded with sufficient confidence. Here, we evaluated the performance of post-CRT MRI in the prediction of pathological nodal status in a cohort of rectal cancer patients. Methods Patients received 45 Gy of radiotherapy in 25 fractions, followed by surgery within six to eight weeks. Post-CRT MR imaging was performed in the week before surgery using a phased array whole body coil and a 1.5 Tesla scanner. Mesorectal nodal status as assessed with MRI was compared with the pathological staging to calculate sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. Results We evaluated 147 patients (mean age 61,5 ± 13 yrs, 71% male). The mean time period between the completion of CRT and MRI was 5.8 weeks. Pathological stage distribution was as follows: stage 0 (ypCR), 18.5%; stage I, 11%; stage II, 29%; stage III, 35%, and stage IV, 6.5%. A median of 9 nodes was evaluated (range 1-27). The nodal downstaging effect of chemoradiation was considerably underestimated by MRI (Table). The performance of post-CRT MRI in detecting nodal involvement was as follows: SE 72.5%, SP 38.2%, PPV 38.2%, NPV 84.5%, and overall accuracy 72.5%. Thus, MRI resulted in post-CRT nodal status overstaging in 43.9% and understaging in 27.5%. Overall actuarial survival was 90%. Conclusion Post-CRT MRI commonly underestimates nodal downstaging, possibly explained by the difficulty to differentiate malignant from inflammatory nodes. In rectal cancer patients with a negative post-CRT MRI scan, 15.5% may harbour residual malignant mesorectal nodes.

Comparison of clinical and pathological stage

N stage	Clinical N stage before CRT N(%)	Clinical N stage after CRT N(%)	ypN stage N(%)
0	25(17)	71(48)	106(72)
1	89(60)	54(37)	29(20)
2	29(20)	22(15)	11(7.5)

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Distance-to-Care: Stage at Diagnosis for New Mexico (NM) Residents with Colorectal Cancer (CRC) M.C. Mason,* A. Bruner, A.W. Meisner, K.T. Morris, I. Nir, C.L. Wiggins, A. Rajput. *Surgery, University of New Mexico, Albuquerque, NM.*

Purpose: CRC is a leading cause of morbidity and mortality among NM's American Indians, Hispanics, and non-Hispanic whites. Previous studies have shown that rural residents are more likely than urban dwellers to be diagnosed with late stage disease. Geographically New Mexico is the 5th largest state with a population of 2 million, many of whom reside in rural regions. This study was designed to characterize the association between distance-to-care and stage of disease at diagnosis in NM. Methods: The population-based NM Tumor Registry was used to identify records for all incident cases of CRC between 2001-2008. Latitude and longitude were determined for the place of residence for cancer cases and for the facility where each case was diagnosed. The "Great Circles" algorithm was used to estimate the distance from place of residence to the diagnosing facility. The percentage of cases diagnosed with early stage vs. other stages (i.e., regional, distant, and unknown stages-combined) was assessed by quartile of distance-to-care with the use of the chi-squared test for trend. Multiple logistic regression was used to characterize the association between stage and quartile of distance-to-care while controlling for other factors know to be associated with stage at diagnosis. Results: Analysis was based on 6,291 incident cases of CRC that were diagnosed among NM residents. Latitude and longitude for both place of residence at diagnosis and location of diagnosing facility were available for 4,385 (69.7%) of all incident cases. The percentage of cases diagnosed at early stage was inversely related to the distance between the place of residence at diagnosis and the facility where the cancer was diagnosed, as follows: 41.4% of cases in Quartile 1 (shortest distance-to-care); 39.9% in Quartile 2; 37.8% in Quartile 3; and 35.3% in Quartile 4 (p=0.002).By multiple logistic regression, distance-to-care was a significant predictor of stage at diagnosis after adjustment of sex, age and race/ethnicity. Conclusions: Rural residents of NM who must travel relatively long distances to receive medical care are at increased risk of being diagnosed at late stage colorectal cancer.

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Inhibition of Nuclear Proteins Export using a Novel CRM1 Inhibitor Increases the Apoptotic Response to SN38 in Colon Cancer H. Chung,* R. Salas Fragomeni, J. Cusack. *Division of Surgical Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

Resistance to conventional chemotherapy remains a major challenge in Stage IV colon cancer. CRM1 inhibition leads to nuclear sequestration of proteins such as tumor suppressor p53, growth regulatory proteins, and chemotherapy targets such as topoisomerase I/II in nucleus. We examined the effects of combination use of KPT185 (a novel CRM1 inhibitor) with SN38 (active metabolite of irinotecan) and the effect of drug administration sequence in human colon cancer cell lines to determine if CRM1 inhibition enhances the cytotoxic effect of chemotherapy. We evaluated the combination effect of KPT185 with SN-38 on both Lovo (KPT-sensitive, IC50 = ~ 500nM) and HT29 cells (KPT-resistant, IC50 = 1000 ~ 3000nM) by the Chou-Talalay method, which is an MTT based assay that interrogates response across a spectrum of drug dosages: KPT185 (0, 1, 10, 100, 1000, 10000 nM) and SN38 (0, 100, 500, 1000 nM). Cell cycle analysis by FACS with propidium iodide (PI) staining was performed. Effects on apoptosis were determined by FACS (Annexin V/PI staining and Cell Death Detection ELISA assay). Chou-Talalay method determined there is synergistic effect when KPT185 is combined with SN38 in both Lovo and HT29 cells (combination index > 1). FACS analysis demonstrated combination use of KPT185 and SN38 induced the increase of the apoptotic sub-G1 fraction and a shift toward G2/M arrest and significantly increased the Annexin V/PI-positive fraction compared with SN38 alone case ($P < 0.05$). Treatment sequence studies demonstrated that pretreatment of SN38 followed by KPT185 (KPT-post) produced the maximum synergistic effect compared with pretreatment of KPT185 following by SN38 (KPT-pre) or concurrent use (KPT-con); Cell Death Detection ELISA assay showed KPT-post increased apoptosis most (4.3-fold) compared with KPT-pre (4.2-fold), KPT-con (3.8-fold) and SN38 alone (1-fold). Our results show KPT185, a novel CRM1 inhibitor, sensitizes the response to SN38 in KPT-sensitive as well as KPT-resistant colon cancer cells. This method of sensitizing colon cancer cells warrants further evaluation in preclinical models of colon cancer.

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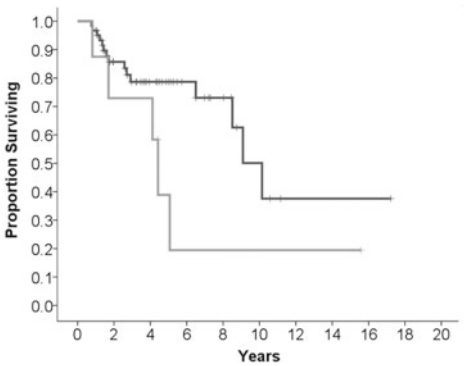
Lymphatic Metastasis in Well-differentiated Appendiceal Cancer: Prognostic Factors and Associations with Outcome J.S. Hill,[1]* S. Rafeeq,[1] M.H. Katz,[1] M.J. Overman,[1] L.A. Lambert,[2] R.E. Royal,[1] P.F. Mansfield,[1] K.F. Fournier.[1] *1. MD Anderson Cancer Center, Houston, TX; 2. University of Massachusetts, Worcester, MA.*

Introduction: Well-differentiated appendiceal adenocarcinomas (WDAA) are rare tumors characterized by peritoneal spread. Lymph node metastasis can occur, yet the association between nodal spread and recurrence is poorly understood. Methods: A single institution retrospective review of patients seen between August 1993 and January 2010 with a pathologic diagnosis of WDAA who underwent colectomy was conducted. Patients with zero lymph nodes found during pathologic review were excluded. Parameters evaluated included demographics, presence of lymph node metastasis, completeness of cytoreduction and time to recurrence. Results: Of 688 patients with appendiceal neoplasms, 160 (23.3%) had WDAA. The mean age at diagnosis was 50.7 years and 81 (50.6%) were male. Median follow-up after diagnosis was 58.5 months. One hundred patients (62.5%) had regional or distant metastasis present at the time of colectomy. Seventy-eight (48.8%) colectomies were performed at outside institutions. The median number of nodes examined was 12. Twelve patients (7.5%) were found to have nodal metastasis. The rate of peritoneal metastasis did not correlate with the presence of nodal metastasis (node positive 9/12, 75% versus node negative 91/148, 61.5%; p=0.35). No difference in the ability to perform complete cytoreduction existed for those with and without nodal metastasis (66% versus 51% p=0.19). Examining patients with complete cytoreduction and ≥ 12 months of follow-up, there was an increased risk of recurrence among patients with lymphatic metastasis compared to those without (5/8, 62.5% versus 15/61, 24.6%; p=0.03). In this subset, median disease-free-survival in lymph node positive patients was 53 months compared to 109.1 months in patients without nodal metastasis (p=0.08)(see figure). Conclusions: Patients with WDAA tumors have an overall favorable prognosis; however, patients with lymph node metastasis appear to have an increased risk of recurrence and apparent shortened disease free survival. Right colectomy may be warranted in this patient population.



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Treatment Results of Inguinal Lymph Node Metastasis from Rectal Adenocarcinoma M. Takawa,* T. Akasu, R. Inada, S. Yamamoto, K. Satoh, . Motohashi, S. Fujita, Y. Moriya. *Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan.*

BACKGROUND: Clinical picture of inguinal lymph node metastasis from rectal adenocarcinoma is unclear and treatment strategy is not established because of limited number of reported cases. Generally prognosis is reported to be poor. To clarify clinical picture and evaluate role of radical groin dissec-

tion, we reviewed our treatment results. METHODS: Between 1991 and 2011, 15 patients with inguinal lymph node metastasis from rectal adenocarcinoma underwent radical groin dissection. We removed the lymph nodes and fat tissue completely from the region surrounded by the inguinal ligament, sartorius muscle, adductor longus muscle, and femoral nerve, artery, and vein. RESULTS: There were 11 men and 4 women with a median age of 62 (39-71) years. Metastasis was metachronous in 12 patients, synchronous in 3, unilateral in 14, and bilateral in 1. Histologic diagnosis included adenocarcinoma in 14 cases and adenosquamous carcinoma in 1. Stages of primary tumor were stage I in 2 patients, stage III in 12, and stage IV in 1 (liver). A median distance between the anal edge of tumor and the anal verge was 1.5 (0-4) cm. Thirteen patients had a primary tumor involving the anal canal. Nine had lateral pelvic lymph node metastasis at initial surgery. A median disease-free interval was 11 (0-45) months. All patients underwent radical groin dissection for inguinal metastasis. Complications included lymphorrhea in 8 patients and wound infection in 1. During a median follow-up time of 3.3 (0.2-9.6) years, 8 patients developed recurrence. The initial site of recurrence included the lung in 6 patients, the external inguinal lymph node in 3, the paraaortic lymph node in 2, the liver in 1, and the brain in 1. One patient died of disease. Four-year overall survival rate was 90%. CONCLUSION: Involvement of the anal canal by a primary tumor and lateral pelvic lymph node metastasis may be risk factors of the inguinal lymph node metastasis. Radical groin dissection may be effective for prolonging survival. Countermeasures for lung and external iliac metastasis are necessary.

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Neoadjuvant Chemoradiotherapy and Multivisceral Resection for Locally Recurrent Adherent Colon Cancer M. Cukier,* H. Soliman, A.J. Smith, S.C. Wong. *Surgical Oncology, University of Toronto, Toronto, ON, Canada.*

Background: Complete resection and locoregional control is challenging in the management of locally recurrent adherent colon cancer (LRACC). There is limited literature on the role of neoadjuvant chemoradiotherapy (CRT) in the management of these patients. Methods: We retrospectively reviewed our institutional Colorectal Cancer Data Base (January 2000 to July 2010) for 15 patients with non-metastatic LRACC who received neoadjuvant CRT followed by multivisceral resection. Patients with a previous primary within 15 cm from the anal verge were excluded. CRT consisted of radiation (45-50 Gy in 25 daily fractions) and concurrent 5FU infusion (225 mg/m2/day) for the duration of radiation. Local control, toxicities, overall survival (OS) and disease-free survival (DFS) were collected. Results: The median age was 59 (range 37-87) with 60% male patients. The median follow-up was 33 months for all patients. The most common site of the original primary was the sigmoid (53%), followed by the left colon (33%). All patients underwent enbloc multivisceral resection. The number of abdominal structures/organs resected ranged from 2 to 5. Postoperative complications developed in 7 patients but no 30-day mortality was seen. All but one patient (small foci in radial margin) had microscopically clear resection margins (R0). Complete pathologic response was documented in 1 patient (7%) and another had minimal residual tumour cells. Seven patients (47%) received post-operative adjuvant chemotherapy. The 3-year OS and 3-year DFS were 87.6% and 63.7% respectively. At last follow-up all patients were alive except one (had local recurrence out of radiation field). Five recurrences (two lung metastases, two out of field recurrences, and one in-field) occurred at an average of 21 months post treatment. Conclusions: A multimodality treatment approach to patients with LRACC using neoadjuvant CRT and en-bloc multivisceral resection results in high rates of R0 resection and excellent local control with acceptable morbidity and mortality.

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Adjuvant Chemotherapy in High-risk Stage II Colon Cancer Patients: (Un)common Practice? B. Koebrugge,[1]* L.N. Van Steenbergen,[2] D.J. Lips,[3] V.E. Lemmens,[2] H.C. Van der Linden,[3] H.F. Pruijt,[3] G. Liefers,[1] C.J. Van de Velde,[1] K. Bosscha.[3] *1. Leiden University Medical Center, Leiden, Netherlands; 2. Eindhoven Cancer Registry, Cancer Center South, Eindhoven, Netherlands; 3. Jeroen Bosch Hospital, 's Hertogenbosch, Netherlands.*

Introduction: A subgroup of stage II colon cancer patients are considered at high-risk for recurrent disease based on tumor obstruction/perforation, T4 lesion, < 10 lymph nodes(<10LNs), lymphangio-invasion or a poorly differentiated tumor. According to ASCO/ESMO guidelines adjuvant chemotherapy (CT) should be considered in these patients. Methods: All patients diagnosed with colon cancer stage II between 2000-2009 were included(n=23,124). The proportion of high-risk patients (based on T4 or <10LNs) receiving adjuvant CT was determined. Determinants of adjuvant CT administration and their impact on survival were analyzed. Results: 6% stage II colon cancer patients received adjuvant CT. Patients aged >75 years received adjuvant CT rarely compared to patients <75(1% vs. 11%; p<0.0001), while patients with a T4 lesion, <10LNs and patients diagnosed more recently, received adjuvant CT more often. Furthermore, there was a large variation in adjuvant CT administration between geographic regions. Adjuvant CT administration increased in all (sub)groups of patients after introducing adjuvant CT for high-risk stage II patients in the guideline in 2005. Of the T4 patients(n=3,064) 31% aged<75 years received adjuvant CT. Crude 5-year survival for T4 patients with and without CT was 71% and 55% respectively(p<0.0001). Multivariate survival analysis for patients with a T4 lesion showed that age >75 years and <10LNs were negative prognostic factors, in contrast to adjuvant CT and male gender. Survival differed by geographic region in patients with a pT4 lesion. Of the patients with <10LNs(n=10,264), 12% aged <75 years received adjuvant CT. Crude 5-year survival for patients with and without CT was 70% and 71% respectively(p=0.19). Multivariate survival analysis for patients with <10LNs showed that age >75years and T4 stage were significant negative prognostic factors of survival, in contrast to adjuvant CT and male gender. Conclusion: Just a minority of high-risk stage II colonic cancer patients received adjuvant CT, with a large variation between geographic regions. Adjuvant CT administration increased since the introduction of the high-risk guideline in 2005.

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Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin as a Treatment for Peritoneal Carcinomatosis Arising from the Appendix E. Marcotte,[2]* P. Drolet,[1] P. Dubé,[1] A. Mitchell,[1] G. Leblanc,[1] Y.E. Leclerc,[1] S. Frenette,[1] L. Sideris.[1] *1. Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada; 2. Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada.*

Introduction: Peritoneal carcinomatosis (PC) arising from the appendix is a rare disease for which the long-term prognosis is poor. The aim of this study was to evaluate the results of an aggressive treatment approach used in our institution in the last 8 years. Methods: Charts from all patients with a PC arising from the appendix were retrospectively reviewed. Treatment consisted of complete surgical cytoreduction of the tumour followed by hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin (460 mg/m^2) at 43°C over 30 minutes. Ronnett's histologic classification was used for tumour grading: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis with intermediate features (PMCA-I) and peritoneal mucinous carcinomatosis (PMCA). Results: From February 2003 to April 2011, 78 patients underwent laparotomy with curative intent. Mean follow-up was 33.7 months. Fifty-eight patients received HIPEC, but 11 patients could not have complete cytoreductive surgery and therefore received no HIPEC. Nine patients with a negative second-look surgery also received no HIPEC. The 5-year overall survival (OS) for the entire cohort was 66.2%; 100% for the negative second-look patients, 77% for the HIPEC patients and 9% for the unresectable patients (p<0.0001). The 5-year disease-free survival (DFS) was 50% for the HIPEC patients and 87.5% for the negative second-look patients. In regards to the 5-year DFS for the HIPEC patients, histologic grade (DPAM 100%, PMCA-I 40%, PMCA 20%; p=0.0016) and completeness of cytoreduction (CCR-0 56%, CCR-1 24%; p=0.0172) were prognostic factors. There was 1 postoperative mortality. The major complication rate for patients treated with HIPEC was 40%, including intra-abdominal abcess (17%), hemorrhage (12%) and anastomotic leak (10%). One patient in the HIPEC group experienced grade 2 neuropathy that lasted for one week following surgery. The same patient also developed grade 3 thrombocytopenia one week postoperatively. Conclusions: This therapeutic approach seems both feasible and safe in selected patients. Recurrence is however frequent and represents a challenge.

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Neoadjuvant Chemotherapy in the Management of Mucinous Appendiceal Carcinomatosis D. Magge,* A. Frances, A. Mavanur, L. Ramalingam, H.L. Jones, M. Holtzman, S. Ahrendt, A. Zureikat, J. Pingpank, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *General Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Peritoneal carcinomatosis of appendiceal origin frequently recurs despite aggressive regional therapies. Systemic chemotherapy is frequently recommended, despite a paucity of data and poor chemo-responsive nature of these tumors. Methods: 23 patients received neoadjuvant chemotherapy prior to undergoing cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of the appendix. Response was evaluated by pre- and post-chemotherapy disease symptoms, CT-scan images, tumor marker levels, and pathologic response. Results: A majority of patients had peritoneal mucinous carcinomatosis (21 patients, 91%), high grade tumors (17 patients, 74%) and recurrent disease (12 patients, 52%). The median duration of chemotherapy was 5 months (IQR=3) and most patients received FOLFOX/FOLFIRI (87%) and/or Avastin (44%). Subjective improvement in disease symptoms occurred in 14 of 19 evaluable patients (74%). CT imaging before and after chemotherapy was available for 17 patients; assessment of "omental cake", ascites and/or abdominal masses demonstrated partial response in 6 (35%), stable disease in 5 (29%) and disease progression in 6 (35%) patients. Pre- and post-neoadjuvant tumor marker levels were available as follows; CEA, 13 patients; CA 125, 3 patients. Five patients (39%) had elevated CEA level prior to chemotherapy; 1 had normalization, 3 had a < 50% reduction and 1 had an increase in CEA level after chemotherapy. Similarly, all 3 patients with elevated CA 125 levels prior to chemotherapy demonstrated normalization or more than 50% reduction in tumor marker level after chemotherapy. Pathology reports were available for 21 patients, with 3 patients demonstrating pathologic response, described as acellular mucin with giant cell reaction. The median overall survival (13 months) after CRS/HIPEC was not influenced by patient response to chemotherapy. Conclusions: 86% of patients demonstrated a response to neoadjuvant chemotherapy by at least one objective measure of disease status. A larger cohort of uniformly treated patients would be required to validate the benefits of neoadjuvant chemotherapy in this malignancy.

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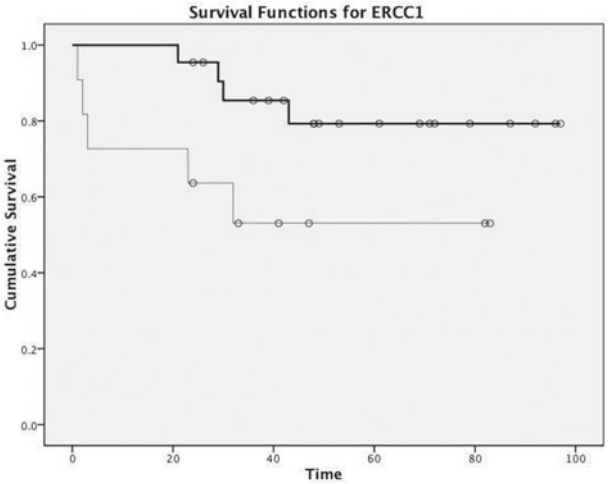
Immunohistochemical Biomarkers Assessment of Stage III Colon Cancer undergoing Sentinel Lymph Node Mapping on Overall Survival and Recurrence S. Saha,[1]* D. Wiese,[1] M. Kanaan,[1] S. Kaushal,[1] S. Nagpal,[1] D. Loesch,[2] R. Ashfaq,[2] A. Alarcon,[2] R. Gerkin,[2] R. Bender.[2] *1. McLaren Regional Medical Center-Michigan State University, Flint, MI; 2. Caris life Sciences, Irving, TX.*

Introduction Sentinel lymph node mapping(SLNM) and biomarkers(BioM) of primary tumors can identify colon cancer (CCa) patients (pts) who may benefit from chemotherapy by providing better nodal staging and poor prognosis. BioM, such as thymidylate synthetase (TS) and ERCC1 can influence 5-FU and platinum-based chemotherapy response. Caris Target Now is an evidence-based tool marrying the relevant literature with Immunohistochemical(IHC) BioM expression, mutation analysis and microarray to provide oncologists of "drugable" targets in each tumor specimen. Methods: We did a retrospective analysis of 33 pts (age 41-84 yrs) with Stage III CCa who had SLNM at a single institution from 2000 to 2007. IHC results for 17 BioM were assessed on pts by scoring the percentage of cells stained along with the intensity of staining in the primary tumor. BioM cutoffs were applied to decide positive and negative staining results. Of 33 pts, 17 received 5FU/Leucovorin, 11 received Folfox and 5 on whom treatment information is unavailable. IHC results were correlated with age, gender, pre-op CEA (0-64), tumor size (1.4-10.0 cm), number of LN (1-21) and OS. Results: For the 33 pts, there was no significant relationship to recurrence for any of the IHC markers, age, gender, tumor size or number of positive LN. With a minimum follow-up of 48 months, the only significant predictor of overall survival (OS) was ERCC1 using a Cox regression analysis (HR=0.25, p=0.042). A Kaplan-Meier plot for ERCC1 revealed a mean OS of 50 months for no expression versus 83.5 months for above threshold expression (p = 0.050)(Figure 1). Patient age was significantly different between these 2 groups (58 vs. 68.9 yrs, p=0.017). Furthermore, there was no correlation between TS and ERCC1 expression (p=0.145) nor TS expression and OS. Conclusion: Individual IHC BioM are not prognostic nor predictive of pts outcome in Stage III CCa treated with 5-FU based adjuvant chemotherapy with the possible exception of ERCC1. Above threshold expression of ERCC1 in our pts was significantly correlated with improved OS and older pts.



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Resection with En Bloc Removal of Regional Lymph Node following Endoscopic Resection for T1 Colorectal Cancer H. Kobayashi,[1]* M. Enomoto,[2] T. Higuchi,[2] H. Uetake,[3] S. Iida,[2] T. Ishikawa,[3] M. Ishiguro,[2] K. Sugihara.[2] *1. Center for Minimally Invasive Surgery, Tokyo Medical and Dental University, Tokyo, Japan; 2. Department of Surgical Oncology, Tokyo Medical and Dental University, Tokyo, Japan; 3. Department of Translational Oncology, Tokyo Medical and Dental University, Tokyo, Japan.*

Background: Various guidelines suggest indications for performing additional colectomy with en bloc removal of regional lymph nodes following endoscopic resection for T1 colon cancer. The aim of this study was to evaluate the outcomes of patients with surgery after endoscopic resection for T1 colorectal cancer. Patients and Methods: We reviewed the data from 275 patients who had undergone curative resection for T1 colorectal cancer at a single institution between 1991 and 2009. We evaluated the rationale for additional surgery after endoscopic resection and the association between clinicopathologic features and lymph node metastasis. Results: Among the 275 patients, 68 had a surgery after endoscopic resection. The 5-year overall survival rate was 96.3%. Reasons for additional surgery included an endoscopic specimen with a pathologically positive margin (n = 20), lymphovascular invasion (n = 25), and depth of submucosal invasion ≥ 1000 μm (n = 23). When endoscopists could not find macroscopic cancer residue during endoscopic resection, no pathologically residual cancer was found in the surgically resected specimens. Six patients (8.8%) had lymph node metastasis in this series. Histologic type other than well differentiated adenocarcinoma was an independent risk factor for lymph node metastasis (P = 0.028). In the absence of lymphovascular invasion, patients with well-differentiated T1 colorectal cancer did not have nodal involvement. Conclusions: Although the outcomes of patients with additional surgery after endoscopic resection for T1 colorectal cancer were satisfactory, excessive and unnecessary surgery may have been performed. Additional surgery after endoscopic resection for T1 colorectal cancer might be unnecessary for patients with well-differentiated adenocarcinoma, and no lymphovascular invasion.

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Preoperative Mild Hypofractionated Accelerated Chemoradiotherapy for Rectal Cancer: An Alternative for High Volume Cancer Centers P. Luna,* N. Velazco, J. Huerta, S. Rodriguez, M. Ramirez. *SURGICAL ONCOLOGY, Hospital de Oncologia CMN SXXI, Mexico D.F., Distrito Federal, Mexico.*

Background. Preoperative short- course radio or chemoradiotherapy followed by surgery (total mesorectal excision) after the next week has been asso-

ciated with low rate of local recurrences in patients with resectable stage II-III. Administration of long courses of preoperative radiation (50.4 Gy in 28 fractions) combined with chemotherapy is reserved for patients with locally advanced tumors results with comparable outcomes in terms of local tumor control, but increasing the dowstaging and anal sphincter preservation rate. Objective. To evaluate the results of hypofractionated accelerated chemoradioterapy in terms of morbidity after treatment, downstaging and anal sphincter preservation. Material and Methods. Patients with locally advanced rectal adenocarcinoma, radiological stage II-III received preoperative hypofractionated accelerated radiotherapy (37.5 Gy/15 fractions) + capecitabine 600 mgs/m2 during radiotherapy and surgery was performed 6 weeks. Results. From January to October, 2009. 53 patients (34 males and 19 females), six were excluded of the study due to: unresectable (3), abandon (3). Mean age was 54.3 years, preoperative CEA was 17 ng. Tumors were located al a mean of 3.9 cm above the anal verge, 35 patients had radiologically positive lymph nodes. Grade 3 toxicity after treatment was: skin, 10.6%; gastrointestinal, 1.9% and hematological, 3.8%. Surgeries were: low anterior resection, 32; abdominoperineal resection, 12 and supralevator pelvic exenteration, 3. In total 74.5% had anal sphincter preservation. Tumor stages were: 0-1 (12.8%), IIA (29.8%), IIB (4.3%), IIIA-B (12.7%), IIIC (21.3%) and IV (6.4%). Morbidity after treatment was: anastomotic leakage (17%), intra- abdominal abscess (8.5%), pelvic sepsis (8.5%), reoperation(12.8%). Mortality 0%. Colostomy was reversed in all patients. Anal sphincter function was preserved in 32/35 patients. Conclusion. Mild preoperative hypofractionated accelerated chemoradiotherapy is associated with similar results to long courses in terms of downstaging, anal sphincter preservation and saving 2-3 weeks of chemoradiotherapy.

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"Extreme" Cytoreductive Surgery for Appendiceal Tumors: Morbidity, Mortality, and Survival P.L. Wagner,* F. Austin, A. Mavanur, L. Ramalingam, H.L. Jones, M.P. Holtzman, S.A. Ahrendt, A.H. Zureikat, J.F. Pingpank, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Multivisceral cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC), is frequently utilized to treat peritoneal carcinomatosis (PC) of appendiceal origin. Some patients require "extreme" surgery due to the volume of disease. It is unclear whether the associated morbidity and mortality is justified by the potential for long term survival. Methods: We divided 275 patients undergoing CRS and HIPEC for appendiceal PC into three groups based on extent of CRS: standard CRS group (n=214) had ≤ 3 organ resections and ≤ 2 anastomoses; "extensive" CRS group (n=61) had > 3 organ resections or > 2 anastomoses; and a subgroup of "extreme" CRS patients (n=10) had ≥ 5 organ resections and ≥ 3 anastomoses. Kaplan Meier survival curves and multivariate Cox-regression models were used to identify prognostic factors affecting outcomes. Results: Compared to the standard group, patients undergoing extensive CRS had a higher median peritoneal carcinomatosis index (16 vs. 13, p<0.0001), OR time (554 vs. 459 min, p=0.0001), blood loss (1200 vs. 750 ml, p=0.002) and length of stay (14 vs. 11 days, p=0.001). No difference in grade, histology, completeness of cytoreduction, grade 3/4 morbidity (32% vs. 23%, p=0.2) or 60-day mortality (1.7% vs. 0.9%, p=0.1) were evident. Compared to the standard group, subgroup analysis of patients undergoing extreme CRS revealed increased median SPCI (16, p=0.012), OR time (645 min, p=0.0001), blood loss 1300 ml, p=0.008) and length of stay (17 days, p=0.02), but no increased grade 3/4 morbidity (5 patients; p=0.07) and no 60-day mortality. Median progression-free (PFS) and overall survival (OS) were 24 and 96 months in the standard group; 18 (p=0.06) and 50 (p=0.8) months in the extensive group; and 40 months and not-reached in the extreme subgroup. In a multivariate Cox-regression model, extent of CRS was not independently associated with PFS or OS. Conclusions: "Extreme" CRS is associated with greater OR time, blood loss, and length of stay, but not higher morbidity or mortality. Extent of CRS is not an independent predictor of survival and may be indicated in patients with good performance status and favorable histology.

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WITHDRAWN

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Hereditary Nonpolyposis Colorectal Cancer in Non-Caucasian Patients M.C. Russell,* M.A. Rodriguez-Bigas, G.J. Chang, J.M. Skibber, B.W. Feig, Y. You. *University of Texas M.D. Anderson Cancer Center, Houston, TX.*

Introduction: Patients with hereditary nonpolyposis colorectal cancer (HNPCC) are at elevated risk for multiple cancers. Studies that characterize HNPCC have been limited to Caucasian patients in Europe and North America, or non-Caucasian patients in their countries of descent. Little is known about HNPCC in ethnically diverse patients living in the U.S. **Methods:** Patients who underwent germline testing (GT) for DNA mismatch repair genes between 1998 and 2011 were identified from a prospectively maintained database at a tertiary-referral cancer center. Patients whose self-reported ethnicity was not Caucasian, and who were the first individuals in their family to undergo GT, were analyzed for: clinical characteristics, tumor microsatellite (MSI) testing, and GT results. **Results:** Fifty-eight unrelated probands (female, 53.4%) met inclusion criteria, including 19 (32.8%) who were Hispanic, 18 (31.0%) African-American, 18 (31.0%) Asian, and 3 (5.2%) Arabic/Other. Amsterdam I, II and revised Bethesda criteria were satisfied in 9 (15.5%), 14 (24.1%) and 43 (74.1%) patients respectively. They were affected by a total of 106 malignancies, at a median age of 48 (interquartile range, IQR: 40-55). Ninety-two (86.8%) were HNPCC-related as defined by the revised Bethesda criteria, most commonly CRC (73.9%), endometrial (10.9%), small bowel (5.4%) and skin (sebaceous neoplasm, 3.3%). The CRCs arose from proximal colon (51.5%), distal colon (25%), rectum (16.2%) or multifocal/other (7.4%), at a median age of 46 (IQR: 38-55). Pathogenic mutations were only detected in a minority of patients. Pathogenic mutations were most frequently detected in patients undergoing MSH6 as guided by tumor studies (Table). **Conclusion:** In ethnically diverse patients, given the substantial proportion of genetic testing considered as VUS or uninformative negative, Bethesda criteria and suggestive tumor studies will identify more patients to be managed as HNPCC than if germline testing were performed alone. These findings emphasize the importance of assessing family history and tumor MSI status in these patients.

	MLH1	MSH2	MSH6	PMS2
Tumor MSI testing by immunohistochemistry				
No. of Patients Tested	56	56	55	48
No. with suggested findings	16	14	22	20
%	28.6	25	40	41.7
Tumor MSI testing by PCR				
No. of patients tested	12	6	11	20
No. with MSI high	11	6	9	15
%	91.7	100	75	75
Germline testing				
No. of patients tested	20	9	7	6
Pathogenic mutation	3	3	3	0
%	15	33.3	42.9	0
Variant of Uncertain Significance	5	3	1	0
%	25	33.3	14.3	0
Uninformative Negative	10	2	3	6
%	50	22.2	42.9	100

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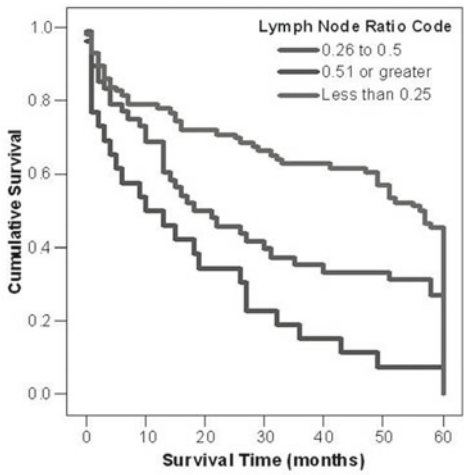
Positive Lymph Node to Recovered Lymph Node Ratio as a Predictor of 5-year Survival in Colon Cancer S. Swistak,* A. Alame, A. Bush, A. Stojcevski, E. Edhayan, R. Berri. *St. John Hospital and Medical Center, Detroit, MI.*

The number of lymph nodes recovered from colon resections for colon cancer is variable despite the best efforts of the surgeon. The ratio of the positive lymph nodes to total number of lymph nodes recovered, referred to as the positive lymph node ratio (pLNR), has been shown to positively correlate with metastatic disease in the South Korean population. Our study assessed the positive lymph node ratio (pLNR) in an American database of colon cancer resections as a predictor of 5-year survival. Our study is a retrospective review of 160 patients that received surgical treatment for colon cancer at a single institution between January 1, 2000 and December 31, 2004. The positive lymph node ratio (pLNR) was calculated. The patients were followed up for a period of 5 years. Data was analyzed for the entire cohort as well as in a smaller subset of patients in whom a minimum of 12 lymph nodes were recovered. For analysis, subjects were then divided into 3 subgroups based on their pLNR status. Group 1 (n=91) had a pLNR of less than 0.25, Group 2 (n=43) had a pLNR of 0.26 to 0.50 and Group 3 (n=26) had a pLNR greater than 0.51. The average length of survival for Group 1, Group 2 and Group 3 was 41 months, 29

months and 18 months respectively (p<0.00005). Only 3 subjects within Group 3 survived the entire 60 month post-op period. When the data was narrowed to only subjects in whom a minimum of 12 lymph nodes were recovered, the overall average pLNR decreased to 0.24 while the mean survival increased slightly to 35.6 months. Three subgroups were again created with the same parameters. Average length of survival for Group 1 (n=58), Group 2 (n=21) and Group 3 (n=11) was 42 months, 31 months, and 14 months respectively (p=0.0001). With a minimum of 12 lymph nodes recovered, there were no survivors at 5 years post-operatively within Group 3. Our study indicates that the pLNR is a good predictor of 5-year survival in colon resections for lymph node positive colon cancer. Ratio-based lymph node staging is easily reproducible and we suggest is a valid prognostic surrogate in lieu of a 12 lymph node resection.



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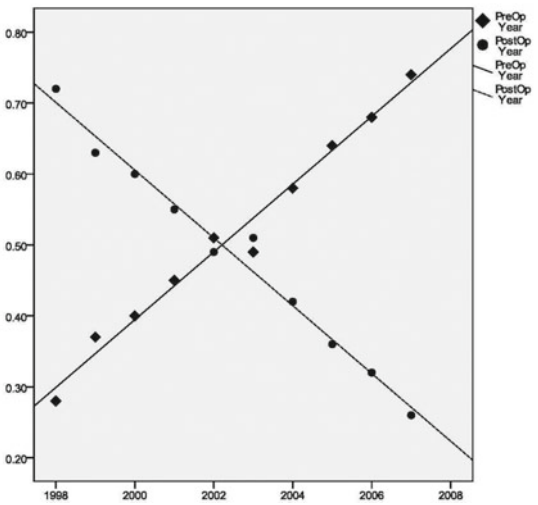
Assimilation of Evidence-based Medicine into Clinical Practice: Adjuvant Radiotherapy in the Multidisciplinary Treatment of Rectal Cancer T.L. Fitzgerald,[1]* T. Biswas,[1] K. O'Brien,[2] E.E. Zervos,[1] J.H. Wong.[1] *1. Surgery, East Carolina University, Greenville, NC; 2. East Carolina University, Biostatistics, Greenville, NC.*

Implementation of evidence based standards is recognized to be problematic. Level 1 evidence supports the superiority of neoadjuvant therapy for stage II/III rectal cancer. The purpose of this study was to determine to what extent evidence based medicine has impacted clinical practice. Methods: Stage II/III rectal cancer patients undergoing surgery from 1998-2007 were identified in the SEER tumor registry using SEER*Stat 6.2. Variables were extracted and analyzed in SPSS; trends were evaluated with regression models and survival with log rank test. Results: A total of 25,129 patients were identified, 15,769 (63%) were treated with adjuvant radiotherapy. A majority were > 60 years old (56%), white (82.8%), male (60.9%), had stage III cancers (59.2%) and treated with neoadjuvant radiotherapy (54.5%). Significant changes in timing of adjuvant radiotherapy were noted over the study period. In 1998 28.1% of patients were treated neoadjuvantly, this increased to 74% in 2007, a 263% increase. Scatter plot best fit lines intersect in approximately year 2002 (figure), p value of trend <0.001. On univarate analysis race (p=0.018), sex (p<0.001), year of diagnosis (p<0.001), age (p<0.001), and stage (p<0.001) were associated increased likelihood of neoadjuvant radiotherapy. Logistic regression found male sex (OR 1.14, p<0.001), year (OR 1.223, p<0.001) and stage II (OR 1.39, p<0.001) were predictors of neoadjuvant therapy. Significant increases in preoperative radiotherapy were observed for all races and cancer stages (p<0.001). There was a significant survival advantage for those treated with adjuvant radiotherapy, median survival 39 vs. 93 months p<0.0001. There, however, was no survival advantage to neoadjuvant vs. postoperative radiotherapy, median survival 94 vs. 93 months, p=0.749. Conclusion: When adjuvant radiotherapy is utilized, there has been rapid adoption of evidence based standards for Stage II/III rectal cancer. However, substantial numbers of patients are not receiving care recognized to improve outcomes.

Figure: Trends in timing of radiotherapy in stage II and III rectal cancer (scatter plot with best fit line) SEER, 1998-2007



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Prognostic Utility of Cyclooxygenase-2 Expression by Colon and Rectal Cancer K.C. Lobo Prabhu,[1]* L. Vu,[1] S. Chan,[2] T. Phang,[3] S. Jones,[2] S.M. Wiseman.[3] *1. University of British Columbia, Vancouver, BC, Canada; 2. British Columbia Cancer Agency, Vancouver, BC, Canada; 3. St. Paul's Hospital, Vancouver, BC, Canada.*

Introduction: To evaluate the utility of cyclooxygenase-2 (COX-2) as a molecular prognosticator for colon and rectal cancer. Methods: Tissue microarrays were constructed using 118 colon cancer and 85 rectal cancer specimens. As well, 44 synchronous metastatic colon cancer lymph nodes, and 22 synchronous rectal cancer metastatic lymph nodes were also evaluated. COX-2 expression was evaluated by immunohistochemistry. Univariate analysis was utilized to determine the prognostic significance of clinicopathologic variables. Results: COX-2 was found to be expressed in 93.2% of colon cancers and 87.1% of rectal cancers. Decreased COX-2 expression was related to decreased disease specific survival (P=0.016) and decreased disease free survival (P=0.019) in the rectal cancer cohort, and this was not observed in the colon cancer cohort. There was no differential expression of COX-2 when comparing primary tumours and their synchronous lymph node metastases. Conclusions: COX-2 expression has prognostic utility in rectal but not colon cancer.

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Long-term Results of Laparoscopic Complete Mesocolic Excision with Central Vascular Ligation (D3) for Colon Cancer T. Akasu,* S. Yamamoto, H. Motohashi, R. Inada, K. Sato, S. Fujita, Y. Moriya, M. Takawa. *Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan.*

Purpose: The short- and long-term safety of conventional laparoscopic dissection for colon cancer is well established. Complete mesocolic excision with central vascular ligation (D3) entails high ligation of the vascular pedicles and complete resection of the mesocolon from the retroperitoneum. We aimed to retrospectively evaluate the long-term outcomes of laparoscopic D3 for colon cancer. Methods: All patients undergoing laparoscopic colectomy with D3 for cecal, ascending colon, sigmoid colon, and rectosigmoid cancers between 2001 and 2010 were assessed using a prospectively maintained database. D3 was performed for patients with clinical stage II or III tumors. Results: Of the 215 patients identified, 105 were male, and 110 female, and 31 had cecal cancer, 50 ascending colon cancer, 101 sigmoid colon cancer, and 33 rectosigmoid cancer. A median age was 64 (29-82) years. A median operating time was 220 (125-408) minutes. A median blood loss was 20 (0-265) mL. There was no blood transfusion, no mortality and 1 conversion. Morbidity was 6.5%. Most complications were treated conservatively. A median hospital stay was 7 (5-56) days. A median number of lymph node harvested was 26 (7-99). There were 3 patients with stage 0 tumor, 48 stage I tumor, 73 stage II tumor, and 91 stage

III tumor. 76% of the patients were correctly staged. 75% of patients with pathologic stage III tumor received 5-FU based postoperative adjuvant chemotherapy. A median follow-up was 3.1 (0.1-9.1) years. Three-year relapse-free survival rate for all patients was 91%. Three-year overall survival rate for all patients was 99%. Those for pathologic stage II tumors were 93% and 95%, respectively. Those for pathologic stage III tumors were 87% and 99%, respectively. Initial sites of recurrence included the liver in 7, the lung in 4, the liver and lung in 1, and the peritoneum in 2. Conclusion: This study suggested short-term and long-term safety of laparoscopic D3 for colon cancer.

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Contrast-enhanced MRI for the Selection of Patients with T1-2N0 Rectal Cancer for Local Excision M. Maas,[1]* J.W. Leijtens,[2] D.M. Lambregts,[1] S.M. Engelen,[1] R.M. Van Dam,[1] I.D. Ayodeji,[1] R.G. Beets-Tan,[1] G.L. Beets.[1] *1. Radiology/Surgery, Maastricht University Medical Center, Maastricht, Netherlands; 2. Laurentius Hospital Roermond, Roermond, Netherlands.*

Aim T1-2 rectal cancer has a 5-20% risk for nodal metastases. Because currently available imaging modalities are insufficiently accurate in nodal staging, additional TME after local excision (LE) of T1-2 tumours is performed in order to minimise the risk for local recurrence (LR). Accurate prediction of N-stage could make additional TME after LE for T1-2 tumors unnecessary. Aim is to evaluate whether contrast-enhanced (CE) MRI can safely select the patients with N0-status after LE. Methods 38 patients with early tumours after LE (26 pT1, 12 pT2) underwent CE-MRI to evaluate N-stage and residual tumour. Local excision consisted of polypectomy (n=17) or transanal endoscopic microsurgery (TEM; 21). The contrast agent was Ultrasmall-Superparamagnetic Particles of Iron-Oxide (USPIO; n=26) or gadofosveset (n=14). A pelvic MRI expert evaluated the MRIs. In case of N0-status, patients were not operated but followed. Patients with N+status underwent TME, with or without neoadjuvant therapy. Results CE-MRI predicted N+status in 3/38 patients. Two of them underwent TME, confirming N+status in one, but refuting N+status in the other (false-positive). The third patient underwent chemoradiation which sterilised the nodes. In 35/38 patients N0-status was predicted. These patients underwent follow-up. Median follow-up was 31 (0-65) months. Four LRs were found: 2 in T2 tumors and 2 in T1-tumors. 3 LRs were luminal and 1 was nodal. All recurrences could be treated with curative intent. One patient died after complications of colostomy closure surgery. 2-year LR-free survival and 2-year disease-free survival are 94%. Conclusion 4/35 patients with T1-2N0 tumors, who were selected for follow-up after LE with CE-MRI had a LR: 2 in T2- tumors and 2 in T1-tumors. CE-MRI possibly reduces the number of nodal recurrences. However, since 3/4 recurrences were luminal, endoscopy remains crucial to identify luminal recurrences. For T1-tumors a combination of CE-MRI with endoscopy leads to adequate local control. For T2-tumors this strategy probably is not sufficient. In these patients with T2-tumors additional therapy (e.g. neoadjuvant (chemo)radiation or TME) is indicated.

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Lymph Node Metastasis in Patients with Early Pathologic T Stage Rectal Cancers: What Does Local Excision Leave Behind? M.C. Russell,[1]* Y. Chiang,[1] B.W. Feig,[1] G.J. Chang,[1] M.A. Rodriguez-Bigas,[1] J.M. Skibber,[1] R. Chagpar,[2] J.N. Cormier,[1] Y. You.[1] *1. University of Texas M.D. Anderson Cancer Center, Houston, TX; 2. University of Western Ontario, London, ON, Canada.*

Introduction There is increasing interest in local excision (LE) for rectal cancer, given the advantages of sphincter preservation and reduced morbidity. However, since lymph node positivity is the main determinant of survival in patients with non-metastatic rectal cancer, residual nodal disease and potential risk of local failure after LE must be considered. We utilized a nationwide cancer registry to establish the incidence of, and predictors for, nodal metastasis in rectal cancers of early pathologic T stages. **Methods** Patients diagnosed with rectal cancers of early pathologic T stages between 1998-2007 were identified from the National Cancer Database (NCDB). These included pT1 or pT2 tumors in patients who had not received neoadjuvant therapy (NT), and ypT0, ypT1, or ypT2 tumors after receiving NT. Among those treated without NT, proctectomy was performed in 22,416 (74.7%) and LE in 7,589 (25.3%). After NT, 7,481 (96.1%) underwent proctectomy and 300 (3.9%), LE. Rates of nodal metastasis were calculated from patients who underwent proctectomy. After stratification by the total number of lymph nodes examined, factors associated with nodal metastases were analyzed among those with a minimum of 12 nodes assessed. **Results** Among patients without NT undergoing proctectomy, the incidence of nodal positivity was 12.5% and 26.8% for pT1 and pT2 tumors respectively. Following NT, nodal positivity rates were 8.6% for ypT0 tumors, 12.9% for ypT1 tumors, and 21.4% for ypT2 tumors. In the stratified multivariate analysis, female sex, age younger than 50, higher T stage, higher histologic grade, mucinous/signet-ring features, and more than 12 nodes examined were all significantly associated with nodal metastases in both patients with and without NT (Table). **Conclusion** Among rectal cancers of early pathologic T stages, the risk of nodal metastasis increases with higher T stage and with greater number of nodes examined, regardless of the receipt of NT. These findings must be carefully deliberated, given the current interests in expanding the role of LE based on pathologic T stage of rectal cancer.

Multivariate Analysis of Predictors of Nodal Positivity in Rectal Cancers Of Early Pathologic T Stages

		p T1, T2 Tumors (No neoadjuvant therapy)		**yp T0, T1, T2 Tumors (After neoadjuvant therapy)**	
		Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Sex	Female	Referent		Referent	
	Male	**0.92**	**0.86-0.99**	**0.82**	**0.72-0.93**
Age (Years)	<50	Referent		Referent	
	≥50	**0.72**	**0.66-0.79**	**0.73**	**0.63-0.84**
T stage	T0	n/a		Referent	
	T1	Referent		**1.63**	**1.24-2.14**
	T2	**2.16**	**1.99-2.35**	**2.75**	**2.21-3.43**
Tumor size	0 -1 cm	Referent		Referent	
	1.1 - 2 cm	**1.29**	**1.08-1.54**	1.03	0.85-1.25
	2.1 - 4 cm	**1.19**	**1.01-1.41**	0.92	0.70-1.19
	> 4 cm	1.39	0.96-1.36	1.88	0.67-1.16
	Unknown	1.10	0.92-1.31	0.78	0.60-1.01
Grade	Low (Moderate-well differentiated)	Referent		Referent	
	High (Poor-Undifferentiated)	**2.07**	**1.88-2.29**	**1.99**	**1.66-2.39**
	Unknown	1.05	0.90-1.24	0.99	0.82-1.21
Pathologic feature	Not mucinous or Signet-ring	Referent		Referent	
	Mucinous or Signet-ring	**1.59**	**1.37-1.84**	**1.66**	**1.31-2.11**
Nodes examined	<12	Referent		Referent	
	≥12	**1.34**	**1.29-1.41**	**1.49**	**1.31-2.11**

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Laparoscopic vs. Open Resection for Rectal Cancer: A Comparison of Short-term Outcomes N. De Rosa,* J. Scarborough, C.R. Mantyh. *Duke University Medical Center, Durham, NC.*

Introduction: Although laparoscopic techniques are used with increasing frequency in surgical oncology, comparison of postoperative morbidity and mortality of laparoscopic versus open resection of rectal cancer has not been extensively examined. Methods: Using the American College of Surgeons-National Surgical Quality Improvement Projects's participant use file 2005-2009, patients were identified who underwent abdominoperineal resection and low anterior resection for rectal cancer. Primary outcomes were 30-day postoperative mortality, major complication rate, and minor complication rate. Secondary outcomes included specific complications, need for reoperation, and postoperative length of hospitalization. Forward stepwise multivariate logistic regression was used to determine the association between surgical approach (laparoscopic versus open) and primary outcome measures after adjustment for a number of preoperative and intraoperative related variables. Results: Of the 2,776 patients who underwent proctocolectomy for rectal cancer, 2,373 (85%) had open (OR) and 403 (15%) laparoscopic resection (LR). Laparoscopic approach was not significantly associated with postoperative mortality (0.5% LR vs. 0.8% OR; Adjusted Odds Ratio (AOR) of mortality 0.59 (95% CI 0.13-2.60), p=0.49) or major complication rate (11.7% LR vs. 13.8% OR; AOR 0.91 (95% CI 0.65-1.28), p =0.60). Laparoscopic approach was associated with significantly lower minor complication rate (16.9% LR vs. 28.0% OR; AOR 0.55 (95% CI 0.41-0.73), p <0.0001), due mainly to a significantly lower incidence of postoperative superficial surgical site infection (8% LR vs.

15% OR, p <0.0001). Patients undergoing LR required significantly longer operative times than patients undergoing OR (273 minutes LR vs. 255 minutes OR, p <0.0001), but significantly shorter length of postoperative hospitalization (median 6 (IQR 4-8) days LR vs. 8 (IQR 6-10) days OR, p < 0.0001). Conclusions: Compared to open resection, utilization of the laparoscopic approach for rectal cancer resection does not significantly affect early postoperative mortality or major complication rates, but may reduce the incidence of minor complications.

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Free of Cost Genetic Counseling for Hereditary Colorectal Cancer: A Pioneer Brazilian Experience B.M. Rossi,* R. Micheli, D.V. Viana, J.C. Oliveira, C. Andrade, R.M. Reis, D.R. Paula, G. Fernandes, A.L. Carvalho, E.I. Palmero. *cancer genetics, Hospital de Cancer de Barretos, Sao Paulo, SP, Brazil.*

Background: Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited predisposition to colorectal cancer, secondary to extensive adenomatous polyposis coli. Current recommendations for APC mutation analysis advise full gene sequencing to identify point mutations as well as the multiplex ligation dependent probe amplification (MLPA) technique to detect large rearrangements. Methods: In this study, genetic evaluation was performed for 24 families (28 patients) from Brazilian Federal Health Insurance (SUS), by a multidisciplinary team including clinical geneticist, oncologist, molecular geneticist, nurse, and psychologist. Results: APC mutations were detected in 18/24 families (75%), being 13 different, 10 of which are in exon 15, including 4 nonsense mutations and 6 small deletions leading to premature termination of the protein (frameshift). The 3 mutations outside exon 15 are located at exon 5 (1 nonsense) and 2 at exon 8 (2 nonsense). The mutation located at codon 1309 (c.3927_3931delAAAGA) was found in one patient. In addition, 2 out of the 13 mutations found were not previously reported. Among the 9 FAP families in which we did not found any APC germline mutations, some affected individuals had less than 100 polyps. In this way, MUTYH analysis should be conducted in those APC-negative families. Conclusions: This is, to the best of our knowledge, the first Brazilian Cancer Center offering, without any cost, to all population at-risk, for any hereditary colorectal cancer predisposition syndrome (including FAP and Lynch Syndromes), genetic counselling, cancer risk assessment, genetic testing, treatment and preventive follow up. The identification and characterization of at-risk patients will enable more objective cancer risk estimates and facilitate personal decisions regarding cancer risk prevention strategies.

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Laparoscopic Colon Cancer Surgery in the Elderly: Results are Similar to Those of Younger Patients K.M. Baldwin,* S.C. Katz, L. Suarez, P. Somasundar. *Surgical Oncology, Roger Williams Medical Center, Providence, RI.*

Introduction: Laparoscopic colectomy for colon cancer offers the possibility of shorter hospital stays, less pain and faster return to activities of daily living when compared to open surgery, and may be particularly beneficial in at-risk patient populations such as the elderly. The present study examines outcomes of laparoscopic colon surgery in patients >70 years of age compared to those <70 years of age. Methods: At a single institution, 67 consecutive laparoscopic colon cancer resections were examined. Right colectomy, left colectomy, sigmoid colectomy and low anterior resection were included. All surgeries were performed by the same three surgeons throughout the study period. Patients were divided based on age (<70 and >70 years). Multiple clinicopathologic variables including adequacy of lymph node harvest, length of stay (LOS), and discharge to home or nursing home were compared between the groups using non-parametric tests. Results: Of 67 patients, 31 (46%) were >70 years old. There were no significant differences between the two groups with regards to gender, types of operations performed, number of nodes harvested (Mean 19.1 vs 17.4 nodes), mortality, or major complications (defined as anastomotic leak, pulmonary embolism, major bleeding, enterocutaneous fistula, and post operative bowel obstruction). Post-operative ileus rates were 5% in the >70 group and 3%, in the <70 group, not statistically different. The wound infection rate was 10.4%, with no difference between groups. Interestingly, mean LOS (6.4 days), time to return of bowel function (4.4 days) and discharge to skilled nursing (19.3 % vs 14.7% p = .745 via chi squared) did not differ either. Conclusions: In this single institution study eliminating surgeon bias, it appears that elderly patients fare well with laparoscopic surgery for colon cancer when compared to younger population. Mortality, major and minor morbidities, LOS, and skilled nursing home placement were similar. Given that higher complication rates and LOS would normally be expected in this age group, it appears that elderly patients may benefit significantly from the laparoscopic approach.

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Accuracy of Computed Tomography in Staging Colon Cancer Patients C.R. Oxner,[1]* R. Nelson,[1] W. Lee,[1] M. Duldulao,[1] R. Wiatrek,[1] S. Chen,[1] A. Pigazzi,[2] J. Kim,[1] J. Garcia-Aguilar.[1] *1. City Of Hope, Duarte, CA; 2. UC Irvine, Irvine, CA.*

Background: Though adjuvant chemotherapy is well-established for treating patients with AJCC Stage III colon cancer, there is growing interest in giving chemotherapy neoadjuvantly for these patients. Since clinical staging to determine eligibility requires accurate preoperative imaging, our objective was to determine whether computed tomography (CT) scans can be used to detect nodal disease in colon cancer patients. Methods: We identified patients with AJCC stage I-III colon cancer who underwent curative resection between 2006 and 2010 at our institution. Patient CT scans were obtained and final radiologic reports were recorded in a database. CT images underwent secondary prospective review by a blinded independent surgeon with the intent to identify mesenteric lymphadenopathy (N+). Clinical staging from the original radiologic report and secondary surgeon review of the CT images were then compared with pathologic staging. Results: Imaging and pathology were available for 67 colon cancer patients. Original radiologic review reported N+ disease in 10 of 67 patients (15%), but final pathology revealed 31 of 67 (46%) patients to be N+. Therefore, radiological review correctly predicted Stage III disease in 10 of 31 (32%) patients. On final pathology, 36 of 67 (54%) patients had no nodal disease (N0). Radiologic reports noted absence of lymphadenopathy in 29 of 67 (43%) patients, thus accurately predicting N0 disease in 29 of 36 (80%) patients. Of 67 studies, 14 (21%) had no mention of lymphadenopathy and were considered N0. Of these 14, 6 were N+ on final pathology. Surgeon review accurately identified N+ disease in 4 of these 6 patients. On surgeon review, sensitivity increased from 32% to 68% while specificity dropped from 80% to 61%, corresponding to a decrease in false negatives from 68% to 32% and an increase in false positives from 20% to 39%. Conclusion: Current clinical staging of colon cancer by CT has low accuracy. However, actively seeking nodal disease improves sensitivity but with minor loss of specificity. Improved radiologic criteria and technology may further increase accuracy in clinical staging of Stage III colon cancer patients who will receive neoadjuvant treatment.

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Clinicopathologic Characteristics of Patients with Appendiceal Adenocarcinoma (AA) and Intra-Thoracic Metastasis J.S. Hill,* S. Rafeeq, D.C. Rice, M.J. Overman, R.E. Royal, P.F. Mansfield, K.F. Fournier. *MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: Appendiceal adenocarcinoma (AA) is a rare disease with a prognosis related to tumor histology. Distant metastases, including those to the lung or pleura, are considered rare. We investigated the clinical characteristics and survival in patients with AA and intra-thoracic metastases. METHODS: All patients with a pathologic diagnosis of AA who were evaluated at a single institution between September 1993 and July 2009 were retrospectively reviewed to identify patients with intra-thoracic metastasis. Parameters evaluated included demographics, histologic subtype and location of thoracic metastasis (parenchyma vs. pleural). Survival was calculated using the Kaplan-Meier method. RESULTS: We evaluated 626 AA patients. Forty-two (6.7%) had intra-thoracic metastases: 24% pleural, 52 % parenchymal and 24% had both. Of those with intra-thoracic metastasis, the mean age at diagnosis was 54 years. Sixty percent were male. Histologic grade was: 19 (45%) low, 13 (31%) moderate and 9 (21%) grade high. Mean follow-up was 6.6 years. Median overall survival from diagnosis of the entire cohort was 5.2 years. Median overall survival by tumor grade: high 1.87 years, moderate 4.1 years, and not reached in low grade tumors (p=0.0001). The median overall survival from time of diagnosis of intra-

thoracic metastasis is 1.44 years with survival by grade as follows: high-0.2 years, moderate-1.2 years, and low grade not reached (p=0.0003). Survival was not dependent on intra-thoracic location. CONCLUSION(S): Intrathoracic metastasis in patients with AA occurs at a higher rate than previously thought, even in low grade tumors. This suggests that thoracic imaging should be considered in patients with AA. Overall survival depends heavily on tumor histology.

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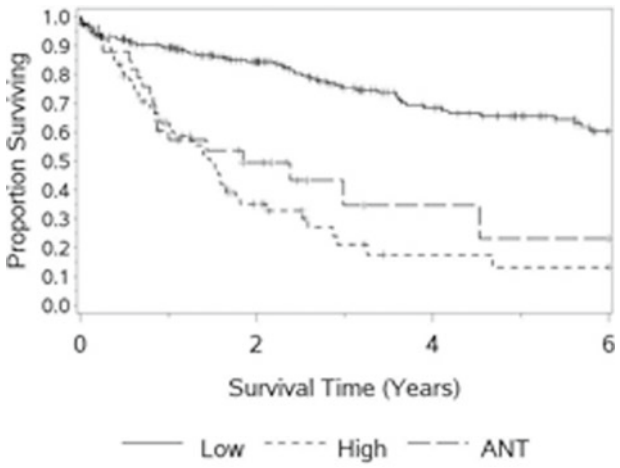
Appendiceal Neuroendocrine Tumors with Peritoneal Surface Dissemination Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy K.F. Griffith,[1]* E.A. Levine,[1] P. Shen,[1] J.H. Stewart,[1] K.I. Votanopoulas,[1] G.B. Russell,[1] K. Geisinger.[2]
1. Department of General Surgery, Wake Forest University Baptist Medical Center, Winston-Salem, NC; 2. Department of Pathology, Wake Forest University Baptist Medical Center, Winston-Salem, NC.

Background: Malignant tumors of the appendix are unusual, and a minority of these are Appendiceal Neuroendocrine Tumors (ANT). ANT frequently presents with peritoneal surface dissemination (PSD). There is a paucity of data regarding the outcomes of these patients. We chose to evaluate the clinical outcomes in patients undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CS-HIPEC) for ANT. Methods: A retrospective analysis of a prospectively maintained database of CRS-HIPEC procedures was performed comparing appendiceal neuroendocrine tumors with other malignant tumors of the appendix. Resection status, recurrence rates, and overall survival were reviewed. All ANT pathologic specimens were reviewed. Results: A total of 33 patients were treated for PSD from ANT with CRS-HIPEC. This data was then compared to 366 patients who were treated for PSD for all other malignant appendiceal tumors with CRS-HIPEC. The 33 with ANT demonstrated an OS 57%, 49%, and 35%, compared to 82%, 70%, and 59% at 1, 2, and 3 years, respectively, p=0.005. Survival (OS) by tumor grade for all data are demonstrated in the graph below [GR1]. All recurrences after CRS-HIPEC were limited to the abdomen. For recurrence data (DFS), the percent recurrence-free at 1, 2, and 3 years in ANT was 59%, 46%, and 40%, respectively, compared to rates of 76%, 66%, and 62%, p=0.01. When comparing ANT to high grade appendiceal adenocarcinomas, no significant difference was discovered in OS (p=0.30) and DFS (p=0.40). Conclusions: ANT are aggressive neoplasms with significant local recurrence rates even after aggressive CRS-HIPEC. Extra-abdominal recurrences were not encountered. Although the prognosis appears worse for these patients when compared to all other malignant neoplasms of the appendix, the outcomes are similar to patients with high-grade appendiceal or colorectal carcinoma. The potential for long-term survival supports the use of CRS-HIPEC in this cohort of patients.



P210

Intraoperative PTH Monitoring Alters Surgeon Decision-making and is Associated with Increased Untoward Events during Failed Parathyroidectomy D.E. Politz,* J.A. Lopez, J.G. Norman. *Norman Parathyroid Center, Tampa, FL.*

Introduction: Monitoring PTH levels during parathyroidectomy (ioPTH) allows surgeons to monitor the progress of the operation. Methods: An 8-year study on 859 cases of failed parathyroidectomy due to a missed adenoma were grouped into those that used ioPTH (584, 68%) and those that did not (NO-ioPTH; 275, 32%). Operative, pathology, and localizing scan reports were reviewed; the surgeon's operative decisions examined. Results: ioPTH was measured 9.2+3.1 times per failed operation (range 4-21). The ability to measure PTH influenced surgeons to remove parathyroid glands as they were found (regardless of appearance) to see the effect on PTH levels, occurring eight times more frequently than in NO-ioPTH cases. Thyroid lobectomies occurred three times more often when PTH could be measured afterwards. A second (unsuccessful) incision was occasionally performed as a direct interpretation of ioPTH. ioPTH operations lasted longer and were associated with three times as many nerve injuries. As an independent variable, the result of preoperative sestamibi had no effect on these outcomes. The missing adenoma was removed from the neck in 97% of cases at subsequent surgery. Conclusions: The ability to measure ioPTH appears to change the way surgeons approach parathyroidectomy, contributing to increased removal of normal parathyroid and thyroid glands and longer, more extensive operations with more untoward consequences. Unexpected ioPTH values may be misleading and encourage surgical decisions that otherwise would not be made.

	io-PTH used	NO ioPTH used	p value
Immediate removal of FIRST parathyroid gland found	448 (77%)	26 (9%)	<0.001
Removal of first TWO consecutive parathyroid glands	153 (26%)	8 (3%)	<0.001
Eventual removal of THREE normal parathyroid glands	53 (9%)	8 (3%)	<0.01
Mean number of parathyroid glands removed per case	2.4 ± 0.6	1.5 ± 0.5	<0.01
Mean number of parathyroid glands found per case	2.6 ± 0.4	2.3 ± 0.5	NS
Thyroid lobectomy	473 (81%)	78 (28%)	<0.001
Contralateral neck not explored prior to thyroid resection (due to ioPTH interpretation)	34 (6%)	0%	<0.01
Second incision (high in neck or sternotomy)	18 (3%)	0	<0.05
OR duration	4.2 ± 0.5 hours	3.1 ± 0.7 hours	<0.001
Recurrent nerve injury	52 (8.9%)	7 (2.4%)	<0.01

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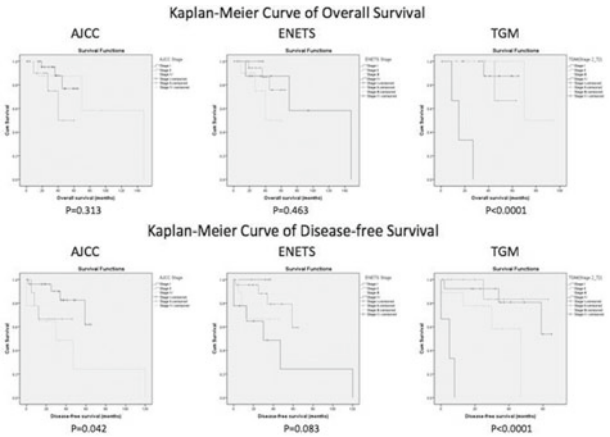
Staging of Pancreatic Neuroendocrine Tumors: Can We Do Better? E.M. Dunki-Jacobs,* C.R. St. Hill, C.R. Scoggins, K.M. McMasters, R.C. Martin, G.G. Callender. *U of Louisville, Louisville, KY.*

INTRODUCTION: Multiple staging systems exist for the classification of pancreatic neuroendocrine tumors (PNETs). The American Joint Committee on Cancer (AJCC) staging manual (7th edition) recently introduced the first TNM staging system which is directly derived from the staging algorithm for exocrine pancreatic adenocarcinoma. This staging system ignores tumor grade - a factor that has been shown to have prognostic relevance. The aim of this study was to evaluate the prognostic validity of the AJCC staging system in comparison to the European Neuroendocrine Tumor Society (ENETS) staging system and a previously proposed Tumor, Grade, Metastasis (TGM) staging system. METHODS: Charts of all patients with pathologically confirmed PNETs treated with surgical resection at the University of Louisville between January 1999 and December 2010 were retrospectively reviewed. Univariate and multivariate analysis was performed; variables included age, sex, presence of hereditary neoplasia syndrome, tumor size and tumor grade. Ki-67 proliferation index and mitotic rate were used to determine tumor grade. Kaplan-Meier analysis of disease-free survival (DSF) and overall survival (OS) were performed for three different staging systems (AJCC, ENETS, TGM) and evaluated using log-rank tests. RESULTS: 49 patients with PNETs underwent surgical resection. Median follow-up was 32.5 months. Ki-67 proliferative index was available for 80% of patients. Tumor grade was a significant predictor of OS (p<0.0001). Five-year DFS and OS were 50% and 74% respectively, with 28% of patients experiencing disease recurrence during the observation period. Analysis of our PNET population using AJCC or ENETS staged groups failed to predict OS (p=0.313 and p=0.463 respectively); however the TGM staging system demonstrated a significant correlation with OS based on

log-rank tests (p<0.0001). DFS was also best predicted using the TGM staging system (AJCC p=0.042, ENETS p=0.083, TGM p<0.0001 - figure). CONCLUSION: Tumor grade is a significant prognostic indicator for PNETs. The incorporation of tumor grade into current staging systems improves the ability to predict prognosis.



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WITHDRAWN

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Surgical Approach and Outcomes in Patients with Lithium-associated Hyperparathyroidism J.L. Marti,[1]* C.S. Yang,[1] T. Carling,[1] S.A. Roman,[1] J.A. Sosa,[1] P. Donovan,[1] M.S. Guoth,[1] K.S. Heller,[2] R. Udelsman.[1] *1. Yale University School of Medicine, New Haven, CT; 2. New York University School of Medicine, New York, NY.*

Introduction Patients receiving lithium therapy are at elevated risk of developing hyperparathyroidism. In lithium-associated hyperparathyroidism (LAH), the incidence of multiglandular disease (MGD) is unclear, and the need for routine bilateral cervical exploration remains controversial. We investigated surgical approaches, pathologic findings, cure rates, and factors associated with persistent or recurrent disease. Methods Multi-institutional, retrospective analysis of 27 patients with LAH undergoing parathyroidectomy with the intraoperative parathyroid hormone (PTH) assay. Univariate comparisons were performed using the Fisher's exact test and t-test. Results Twenty-two (81%) of patients were female, with a median age of 62 years. Median duration of lithium therapy was 20 years. Correct lateralization of lesion(s) occurred in 52% of sestamibi scans and 41% of sonograms. Cervical exploration was unilateral in 9, bilateral in 18 (3 were converted from unilateral). Eight (30%) of patients had surgery performed under cervical block without general endotracheal anesthesia. Sixteen (62%) patients had MGD: 12 with four gland hyperplasia and 4 with double adenomas. Ten (38%) patients had a single adenoma. Twenty-five of 27 patients (93%) had initially successful surgery. The median postoperative follow-up was 7 months. Of the 17 patients with >6 months of follow-up, 2 had persistent disease, and 2 recurred. All patients with a single adenoma remain free of disease. Most patients with persistent/recurrent disease had MGD and were on lithium at the time of surgery. Patients with persistent/recurrent disease were older (p=0.01) and had experienced a longer duration of hypercalcemia (p=0.04). Conclusion LAH patients have a high incidence of MGD, and bilateral exploration is frequently necessary. With access to the intraoperative PTH assay, it is reasonable to initiate a unilateral approach, as a significant proportion of patients will harbor single adenomas and can be reliably cured. It is possible that HPT was sporadic in these patients. Patients with MGD remain at higher risk of persistent/recurrent disease.

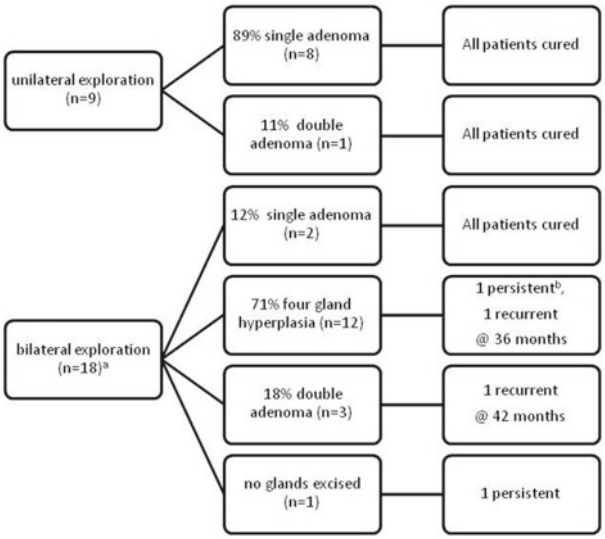

Figure. Operative approach & outcomes of multi-institutional study population (n=27).
Recurrent or persistent disease occurred in 4/27 (15%) of entire population, and 4/17 (24%) of patients with >6 month follow-up.
(a)Three cases began as unilateral explorations.
(b)Intraoperative PTH decreased from 139 to 56 in this patient

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Comparative Analysis of Long Term Outcomes of Elderly Patients Undergoing Total Thyroidectomy for Endemic Multinodular Goiter K.G. Lasithiotakis,* E. Grisbolaki, M. Venianaki, A. Andreou, U. Zoras, G. Chalkiadakis. *Department of General Surgery, University Hospital of Heraklion, Heraklion, Greece.*

Introduction: Thyroid cancer becomes more prevalent with increasing age whereas little is known regarding the long term results of thyroid surgery in elderly patients. The aim of this study was to assess the prevalence of thyroid cancer and the long term outcomes of patients older than 65 years undergoing total thyroidectomy for endemic multinodular goiter. Methods: We retrospectively assessed demographics, clinical presentation, pathological characteristics and long term postoperative outcomes of all consecutive patients undergoing total thyroidectomy for multinodular goiter between January 1990 and October 2008. All thyroid cancer patients underwent telephone interview with the use of structured form. Results: Among 1161 patients included in the study, there were 183(15.7%) patients older than 65 years. Elderly patients presented with larger goiter but the prevalence of thyroid cancer was not significantly different than younger patients (21.4% vs. 23.1%, P=0.970). The histological subtype was similar between age groups but the median diameter of the tumors was slightly lower in the elderly (0.3cm vs. 0.5cm, P=0.049). Postoperative hypocalcaemia was significantly more common in the elderly cancer patients (38.6% vs. 23.7%, P=0.041) and there was a trend towards higher rates of postoperative hoarseness in the older age group (38.6% vs. 25.6%, P=0.080). Within a median follow-up time of 78.5 months similar rates of disease recurrence (90.7% vs. 93.2%, P=0.587) and mortality (2.3% vs. 1.0%, P=0.439) were noted between patients older and younger than 65 years. Conclusion: The prevalence of thyroid cancer in patients undergoing total thyroidectomy for multinodular goiter is similar between patients older and younger than 65 years old. Older patients present with smaller tumors but develop more often postoperative complications compared with their younger counterparts.

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Clinical Utility of 18F-FDOPA in Von Hippel-Lindau Syndrome
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Background: Von Hippel-Lindau (VHL) syndrome is an inherited cancer syndrome in which patients are at risk of developing multiple tumors in different organs. 6-L-18F-fluorodihydroxyphenylalanine (18F-FDOPA) PET is a relatively new metabolic imaging tracer proposed for the use of localizing sites of neuroendocrine tumors. There is limited data of the clinical utility of using 18F-FDOPA PET for identifying neuroendocrine tumors in a high-risk population such as VHL. The aim of this prospective study was to determine the utility of 18F-FDOPA PET in patients with VHL. Methods: Radiologic findings were prospectively collected from four imaging modalities - computed tomography (CT), magnetic resonance imaging (MRI), 18F-FDG PET and 18F-FDOPA PET. 18F-FDOPA PET findings were compared with those from other imaging modalities, as well as with clinical and laboratory data and pathology findings if patients underwent an operation. Results: In 52 patients with VHL, 18F-FDOPA PET identified 20 pancreatic and 20 extra-pancreatic tumors, including lesions in the adrenal gland (n=11), kidney (n=3), liver (n=4), lung (n=1) and a cervical paraganglioma. These tumor sites were not seen by conventional imaging studies in 9.6% of patients and 4.4% of lesions. Seven of 8 patients who had an 18F-FDOPA PET positive lesion underwent resection and pathology showed neuroendocrine tumor. Four of 10 patients with positive adrenal uptake had elevated catecholamine levels, and 6 of 10 patients had a discrete mass on axial imaging. Conclusions: 18F-FDOPA PET may be a useful complementary imaging study in patients with VHL suspected to have neuroendocrine tumors.

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4D Computed Tomography with Specialized Volume Rendering as a Pre-operative Localizing Tool for Primary Hyperparathyroidism
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Background: Primary hyperparathyroidism is caused by a single adenoma in the majority of cases, and a variety of imaging modalities have been used for preoperative localization. We have evaluated a modified 4D-CT approach with specialized volume rendering as a preoperative imaging modality in patients with primary untreated hyperparathyroidism. Methods: A total of 49 patients underwent parathyroidectomy for primary hyperparathyroidism from August 2010 to September 2011. Preoperative modified 4D-CT with specialized volume rendering was utilized and compared to intra operative findings/anatomic pathology as well as ultrasound and sestimibi SPECT. The volume rendering allowed reconstruction of the adenoma in the 3-D images with superimposition of the abnormal gland on the thyroid and other bony/vascular landmarks for surgical guidance. Correlations were determined for calcium and intact parathyroid hormone pre- and post-operatively. Chi squared and Kappa agreement testing were performed. Results: Comparison of modified 4D-CT with specialized volume rendering to intra-operative findings revealed a sensitivity of 100% and a p value of <0.001. Further testing produced a Kappa coefficient of 0.628, indicating a high degree of agreement between modified 4D-CT and intra-operative findings. In contrast to modified 4D-CT, sestimibi SPECT and ultrasound had sensitivities of 56% and 34% and specificities of 67 % and 67% respectively (Table 1). When the sensitivity of modified 4D-CT was compared to the sensitivities of ultrasound and sestimibi SPECT, p values were both <0.001. Comparison of pre and post-operative calcium levels and pre and post-operative intact parathyroid hormone levels demonstrated a p value of <0.001, demonstrating a significant surgical cure rate. Conclusion: 4D-CT with volume rendering has significant correlation with intra operative findings and significantly higher sensitivity when compared to ultrasound or sestimibi SPECT.

Table 1: Descriptive Statistics by Correlate CT

		Yes	No	Overall	Pval
Overall Crt	N	32 (84.2)	6 (15.8)	38 (100%)	
4D CT	Yes	32 (100.0%)	3 (50.0%)	35 (92.1%)	<.001
	No		3 (50.0%)	3 (7.9%)	
Ultra Scan	Yes	11 (34.4%)	2 (33.3%)	13 (34.2%)	0.961
	No	21 (65.6%)	4 (66.7%)	25 (65.8%)	
Sesti	Yes	18 (56.3%)	2 (33.3%)	20 (52.6%)	0.302
	No	14 (43.8%)	4 (66.7%)	18 (47.4%)	

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19-hydroxywithaferin A, A Novel Naturally Occurring Withanolide that Inhibits Medullary Thyroid Cancer Cells through Inhibition of RET Activity and Modulation of the mTOR Pathway A.K. Samadi, B.N. Timmermann, M.S. Cohen.* *Surgery, University of Kansas Medical Center, Kansas City, KS.*

Introduction: Medullary thyroid cancer (MTC) comprises up to 5-9% of all thyroid cancers and is caused by gain of function mutations of the RET protooncogene. Patients with systemic disease continue to demonstrate poor long-term survival warranting the need for novel therapies. The purpose of this study is to evaluate the naturally-occurring withanolide, 19-hydroxywithaferin A (19-HWA), as a novel drug for MTC which targets RET activity and the mTOR pathway in vitro. Methods: Medullary thyroid cancer cell lines TT and DRO81-1 cells were treated with increasing concentrations of 19-HWA. Cell viability/proliferation was evaluated using MTS/trypan blue assays respectively. Apoptosis was determined using flow cytometry and confirmed using Western blot analysis. Long term cytotoxicity on MTC cells was determined by clonigenic assay. Modulation of RET tyrosine kinase and downstream signaling proteins including RAF,MEK,ERK1/2 and PI3Kinase/Akt/mTOR pathways was evaluated by Western analysis. Results: 19-HWA significantly inhibited MTC proliferation(IC50=1.91μM for TTcells and 2.29μM for DRO81-1 cells). Trypan blue determination showed that 19-HWA reduced cell proliferation at 500nM in TT cells and 1000nM in DRO81-1 cells. 19-HWA induced apoptosis in MTC cells in a concentration and time dependent manner. 19-HWA increased annexin v staining by 20% at 2.5 μM and 30% 5.0 μM in DRO81-1 cells. Western blot analysis showed that 19-HWA induced caspase 3 activation and PARP cleavage at IC50 levels in both MTC cells. 19-HWA inhibited phospho-RET and phospho-Akt by 50% as well as total RET and total Akt levels in DRO81-1 cells at IC50 concentrations. Total ERK1/2 levels were not modulated with treatement while phospho-ERK1/2 was increased at 2X IC50. Conclusion: 19-HWA is a potent inhibitor of MTC cells in vitro and its mechanism of anti-cancer activity in these cells in part through inhibition of RET activity and the PI3Kinase/Akt/mTOR pathway. This novel therapeutic warrants further translation to determine its future role in treating MTC patients.

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Neoadjuvant Chemotherapy in 16 Patients with Locally Advanced Papillary Thyroid Carcinoma – A Phase 1 Study N. Besic,[1]* M. Auersperg,[1] A. Perhavec,[1] H. Besic,[1] B. Gazic.[2] *1. Surgical Oncology, Institute of Oncology, Ljubljana, Slovenia; 2. Pathology, Institute of Oncology, Ljubljana, Slovenia.*

Background and Objectives: It is believed that chemotherapy (ChT) is ineffective in papillary thyroid carcinoma (PTC). The aim of our retrospective chart review was to find out if neodjuvant ChT before thyroid surgery had any effect on the size of primary tumor in patients with PTC. Methods: In the period 1976–2006, 1,207 patients were treated for PTC at our Institute. The study included 16 patients (13 women, 3 men; mean age 63.5 years) with PTC, who were treated with neoadjuvant ChT from 1988-2005. Poorly differentiated PTC, classical PTC, follicular variant of PTC and Hürthle cell variant of PTC was diagnosed in five cases, five, three and three cases, respectively. A mean tumor diameter was 9.9 cm (range 5-22 cm). Seven patients had pT4 tumor. Regional metastases were detected in ten patients and distant metastases in seven patients. ChT consisted of Vinblastine in eleven cases, Vinblastine with Adriamyin in two cases and other schedules in three cases. Three patients were treated also with preoperative external irradiation. Results: Altogether, 40 cycles of ChT were given. After ChT tumor size decreased in all 16 patients: for more than 50% in seven (= 44%) patients and for less than 50% in nine patients. R0, R1 and R2 resection was performed in two, ten and four cases, respectively. Median survival of our patients was 92 (range 11-240) months. Six patients are still alive (median survival 157 months) and two of them have no evidence of disease. Two patients died of causes not related to carcinoma, while eight patients died of PTC (five of distant metastases, one of locoregional disease, two of distant metastases and locoregional disease). Conclusions: Neoadjuvant ChT before thyroid surgery may be effective in patients with locally advanced PTC. After neoadjuvant ChT, in 44% of our patients the tumor size decreased for more than 50%.

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Correlation of Preoperative Imaging with Operative Approach in Adrenocortical Carcinoma A.L. Amin,[1]* T.S. Wang,[1] H. Mazeh,[2] A.B. Froyshteter,[2] T.J. Wade,[1] R.S. Sippel,[2] H. Chen,[2] D.B. Evans,[1] T.W. Yen.[1] *1. Medical College of Wisconsin, Milwaukee, WI; 2. University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Imaging (CT and MRI) characteristics and tumor size are used to predict the likelihood that an adrenal nodule represents an adrenocortical carcinoma (ACC). The operative management of ACC includes a wide resection of the tumor when possible, a technique not necessary for most benign adrenal neoplasms. The purpose of this study was to correlate imaging characteristics for adrenal nodules with operative approach and final pathology. Methods: Multi-institutional, retrospective review of patients who underwent adrenalectomy between February 2001 and April 2011. Data reviewed included presenting symptoms, laboratory values, imaging findings, operative approach and final pathology. Imaging characteristics were not consistently reported for all patients. Results: Adrenalectomy was performed on 278 patients for 283 nodules. The mean age was 53 years and 59% were women. Of the 283 nodules, 184 (65%) were incidental, 174 (61%) were functional, and 91 (32%) were both incidental and functional. On final pathology, 9 (3%) patients had ACC (Table). ACC was suspected preoperatively in 5 patients; all had tumors >5 cm, suspicious imaging features, and hormone production; 4 were thought to be benign and of these, 1 was functional. Of the 239 benign tumors, 128 (54%) were > 4 cm on final pathology and 42 (33%) had at least 1 suspicious imaging feature. Suspicious imaging characteristics for ACC had high specificity (70-100%) but low sensitivity (12-50%). Of the 9 patients with ACC, 3 were approached laparoscopically (all unsuspected). At a median follow-up of 25 months (range: 8 – 97 months), 4 patients have died of disease; 2 after laparoscopic approach and 2 after open adrenalectomy. Conclusion: The majority of adrenal tumors (including those >4 cm in size) will be benign, for which the technical aspects of tumor resection are of modest clinical significance. In contrast, suspicious preoperative imaging characteristics may alert the surgeon to the risk for ACC in which case a margin negative resection without tumor spillage is a necessary component of a curative treatment approach.

Imaging characteristics, sensitivity and specificity of 248 adrenal nodules

	Suspected ACC (n=5)	Unsuspected ACC (n=4)	Benign tumors (n=239)
Median tumor size (cm;range) CT MRI Final pathology	 9.5 (5.5-11) 9.3 (8-10.9) 10.5 (6.4-12)	 4.9 (4.3-5.5) 6.7 6 (4.9-8.5)	 3.5 (0.5-17) 3.2 (1-16) 4.3 (0.4-17.5)
CT characteristics (SD	n = 4	n = 4	n = 218
Mean pre-contrast HU	41	48	23 (14.6)
Mean post-contrast HU	84	56	58 (29.8)
<50% washout	1 (25%)	0	39 (18%)
Poorly defined border	1 (25%)	0	1 (0.5%)
Tumor necrosis	3 (75%)	0	10 (5%)
Suspiciousfor local invasion	4 (100%)	0	2 (1%)
Abnormal lymph nodes	3 (75%)	0	2 (1%)
MRI characteristics	n = 3	n = 1	n = 65
Bright on T2	2 (67%)	0	19 (29%)
Poorly defined border	1 (33%)	0	2 (3%)
Tumor necrosis	3 (100%)	1 (100%)	5 (8%)
Suspicious for local invasion	3 (100%)	0	0
Abnormal lymph nodes	1 (33%)	0	0

Excludes 35 cases: 32 adrenal metastases, 1 primary neuroendocrine tumor and 2 malignant pheochromocytomas. Not all imaging characteristics were reported on each patient.

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Technical Variations in the Conduct of Thyroidectomy and Parathyroidectomy Amongst Surgeons - A Survey Study L.R. Henry,[1]* L.B. Helou,[2] N.P. Solomon,[3] A. Chang,[3] S. Libutti,[4] A. Stojadinovic.[3] *1. Indiana University Health/Goshen Center for Cancer Care, Goshen, IN; 2. University of Pittsburgh, Pittsburgh, PA; 3. Walter Reed Army Medical Center, Washington DC, DC; 4. Montefiore Medical Center, New York, NY.*

Background: Heterogeneity of surgical technique exists regarding the conduct of thyroidectomy/ parathyroidectomy. We sought to identify treatment patterns among surgeons conducting the operations. Methods: A survey was designed and beta-tested on five surgical oncologists and then disseminated electronically to members of the American Association of Endocrine Surgeons (AAES) and American College of Surgeons (ACS). Survey results were collected, tabulated and analyzed. Responses among groups were compared using T tests. Significant responses were subsequently analyzed further using generalized linear models to ascertain if significance remained with control of covariates. Results: Of 420 initial web survey visits, 236 (56.2%) surveys were completed. The majority of respondents reported being 'fellowship trained', experienced and 'high-volume' surgeons. The most common fellowship trainings were endocrine (45%), oncology (22%), head & neck (13%), or combinations of the three fellowships (14%). Most surgeons reported that they dissect the course of the recurrent laryngeal nerve (RLN) without using neuromonitoring. Nearly a third of respondents reported routinely using the Harmonic scalpel during the conduct of the operations. Significant differences emerged regarding operative technique according to residency training type, fellowship training, surgeon volume, and practice setting, but only those associated with residency training type and annual surgeon surgical volume remained significant within a multivariate model. Conclusion: Most surgeons who responded to this survey do not routinely use RLN neuromonitoring and most dissect the RLN during thyroidectomy. There are multiple variations in technique according to surgical training, surgeon volume, experience, and practice setting; however, residency training type and surgeon volume appeared most influential in determining surgeons' approaches to thyroidectomy and parathyroidectomy.

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Pheochromocytomas: Are They Still the 10% Tumor? M.E. Hogg,[1]* M.T. Stang,[1] K.L. McCoy,[1] M.J. Armstrong,[1] D.L. Thull,[1] S.M. Challinor,[1] J.H. Yim,[2] J.B. Oglivie,[3] D.L. Bartlett,[1] S.E. Carty,[1] L. Yip.[1] *1. University of Pittsburgh, Pittsburgh, PA; 2. CIty of Hope, Duarte, CA; 3. New York University, New York City, NY.*

Introduction: Pheochromocytoma (Pheo) has long been considered the "10% tumor". Recently, improved imaging and genetic testing have modified management algorithms. We examined a contemporary series of patients with apparent sporadic Pheo to assess for changes in the rates of bilaterality, malignancy, and association with inherited syndromes. Methods: After IRB approval, we identified patients who received adrenalectomy (Ad) for pathologically confirmed Pheo from 1/1990-12/2010. Patients known preoperatively to have the following hereditary syndromes were excluded: Von-Hippel Lindau (VHL), MEN2A or 2B, or neurofibromatosis type 1 (NF1). Pheo was classified as malignant when lymph node and/or distant metastasis were present either histologically or by abnormal MIBG uptake with elevated urine or plasma metanephrines. Results: Initial Ad was performed in 74 patients; 12 patients from an early cohort (1990-99) and 62 patients from a late cohort (2000-10). At presentation, 7 patients (9%) had bilateral Pheo with equal incidence in both cohorts (p=.4). Gene testing for VHL, RET, SDHD, and SDHB was completed in 13/62 late cohort patients and showed a mutation in 5 (38%); 3 patients met clinical criteria for NF1; and 1 patient from the early cohort was later identified as the proband for familial paraganglioma syndrome. Overall, a hereditary syndrome was identified in 9/74 (11%) patients, and was diagnosed in 5/7 patients (71%) with bilateral Pheo. With mean follow-up of 44 months, malignant Pheo has been diagnosed in 4 (5%) patients and was more common in the early cohort (17% v. 3%, p=.06) who had longer follow-up (mean, 87 mo v. 32; p=.003). Conclusions: In this large longterm series, apparent sporadic Pheo was associated with a 9% bilaterality rate, an 11% hereditary rate, and a 5-17% malignancy rate, suggesting that despite increased prevalence of incidental adrenal lesions identified by modern imaging modalities, the 10% rule still appears accurate. A higher rate of malignancy may yet be uncovered by longer follow-up. Inherited syndromes are common when bilateral Pheo is present, but are also diagnosed in patients with unilateral tumors and genetic testing should be considered for all Pheo patients.

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Obturator Canal Lymph Node Metastasis from Rectal Carcinoid Tumor—-Total Mesorectal Excision May be Insufficient for Some Rectal Carcinoids Y. Wang, M. Hall.* *Louisiana State University Health Sciences Center Department of General Surgery Division of Surgical Oncology, New Orleans, LA.*

BACKGROUND: The optimal treatment option for rectal carcinoid tumor remains unsettled. Trans-anal excision has been accepted for small tumors (< 1-2 cm in size) without lymph node involvement. Larger tumors, and those with lymph node metastasis, however, are usually treated via low anterior resection (LAR) with total mesorectal excision (TME). Midgut carcinoid tumors

have been found to have the tendency to obstruct lymphatic flow and create a detour in lymphatic passage. We hypothesize that rectal carcinoid may have similar potential to develop alternative lymphatic pathways outside of the mesorectal envelope, thus escaping surgical removal with traditional TME. METHODS: A retrospective chart review of rectal carcinoid patients who underwent radical LAR with TME between 2006 and 2011 was conducted to determine if any extra-mesorectal metastasis had occurred. RESULTS: 19 patients who underwent LAR with TME for rectal carcinoid were identified. 14 patients had radio-guided surgery (RGS). 12 of which, were injected with TC-99 intra-operatively and 2 had a preoperative injection of In-111 for octreotide scan. 6 of the 19 patients (31.5%) were found to have obturator canal lymph node metastasis, confirmed by final pathologic review. 5 of these 6 patients had the nodal metastasis to the right obturator canal. Of note, 4 of the 6 patients complained of debilitating foot and medial thigh pain on the affected side, with complete symptom resolution after surgical excision. CONCLUSION: Up to 31.5% of rectal carcinoid patients can have extra-mesorectal lymph node metastasis that could easily be missed by the traditional TME. Preoperative octreotide scanning with In-111 injection or intra-operative Tc-99 peri-tumor injection, with concomitant RGS can easily identify and remove such metastasis. Symptomatic improvement can be accomplished with its removal. The effect of such extra-mesorectal metastasis on patients' long term or disease free survival is yet to be determined.

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WITHDRAWN

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A Comparative North American Experience of Robotic Thyroidectomy in a Cancer Population N.R. Jackson,[1]* S.I. Noureldine,[1] L. Yao,[2] S.A. Massasati,[1] E.H. Kandil.[1] *1. Tulane University School of Medicine, New Orleans, LA; 2. Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.*

INTRODUCTION Robotic thyroidectomy is gaining popularity in North American practice. The aim of this article is to explore the efficacy of robotic thyroidectomy in a North American cancer population as compared with the conventional cervical approach. METHODS A retrospective analysis of our prospective endocrine surgery database at a tertiary care center was performed. We included fifty thyroidectomy procedures for the treatment of thyroid cancer that were performed by a single surgeon. Clinical characteristics, tumor size, pathologic type, surgical outcome, postoperative stimulated Thyroglobulin and length of hospital stay of the robotic thyroidectomies were compared with those of the conventional open thyroidectomies performed during the same period. RESULTS Twenty procedures were performed using the robotic gasless transaxillary approach, and thirty using the conventional cervical approach. Average size of cancer (SD) was 1.16 cm (1.39) in the robotic group and 1.7 cm (2.05) in the open group. The average total operative time (SD) for the robotic group was 127.2 (65.6) minutes, 53.6 minutes less than that of the open group, which was 180.8 (132.5) minutes. No robotic cases required conversion to the conventional cervical approach or reoperation for recurrent disease. All robotic cases had margins negative for malignancy on permanent pathology. No significant postoperative morbidity or mortality occurred and all robotic procedures were performed on an outpatient basis. There were no instances of permanent vocal cord palsy on postoperative laryngoscopy. Postoperative stimulated Thyroglobulin levels were not significantly different between the two groups. CONCLUSION Robotic thyroidectomy via a gasless, transaxillary approach is feasible, safe and has similar oncological outcomes as open thyroidectomy in the North American thyroid cancer population and can be performed as an outpatient procedure.

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Utility of BRAF Mutation Detection in Fine Needle Aspiration of the Thyroid M.A. Jones,* D.C. MacGillivray, S. Conus, H. Webber. *Maine Medical Center, Portland, ME.*

Papillary carcinoma is the most common thyroid malignancy and mutation of the BRAF gene characterizes this tumor. The utility of mutational testing as an adjunct to thyroid fine needle aspiration is controversial. After preparation of routine cytology, DNA was extracted from ThinPrep vials in 426 consecutive thyroid FNAs and subjected to polymerase chain reaction to detect the V600E mutation of the BRAF gene. The cytologic smears were interpreted using Bethesda nomenclature without knowledge of the mutation results. Testing was successful in 419/423 (99.1%)samples. The percentage of aspirates positive for BRAF mutation by cytologic category were as follows: Unsatisfactory - 9.8%; Benign - 3%; Atypical - 0%; Suspicious for papillary carcinoma - 50%; Suspicious for follicular neoplasm - 4%; Positive for papillary carcinoma - 86%. In cases with surgical(tissue) follow-up, the mutation positive predictive value for carcinoma was 89%, however 55% of these were in cytologic categories that require surgical removal(positive or suspicious). The sensitivity for carcinoma was 63%. One of the positive cytologies was negative for BRAF and this case was a false positive cytology on surgical excision. In the suspicous for follicular neoplasm category, only one case was positive for BRAF and this was a papillary carcinoma on excision suggesting the mutational assay was more accurate than the cytology. Two patients with unsatisfactory cytologies and positive BRAF mutations had tissue follow-up, one was negative for tumor and one had papillary carcinoma. In this study, the mutational assay had a high positive predictive value as in previous studies but there was no utility for BRAF mutation detection in resolving atypical cytologies. It may have a role in indicating which cases that are suspicious for follicular neoplasms are,in fact,papillary carcinomas. It is not useful in cases with positive or suspicious for papillary carcinoma cytologies. The utility in unsatisafactory or benign cytologies is the subject of an ongoing cost/benefit analysis and further follow-up.

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Epidemiology of Rectal and Small Intestinal Carcinoids: Two Distinct Tumors? S. Taghavi,[1]* S.N. Jayarajan,[1] J.P. Gaughan,[2] A.I. Willis.[1] *1. Temple University Hospital, Philadelphia, PA; 2. Temple University School of Medicine, Philadelphia, PA.*

Intro: Gastrointestinal carcinoids (GIC) are most commonly found in the small intestines. However, in this era of screening colonoscopy, the incidence of rectal carcinoids (RC) is increasing. The aim of this study was to determine if differences exist between these two most common carcinoid tumors. **Methods:** Small intestinal and rectal cancers were reviewed from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 2000-2007. Factors reviewed included age, gender, ethnicity, and survival. **Results:** 12,931 small intestinal cancer tumors (SIT) included 4,731 (36.6%) small intestinal carcinoids (SIC). 57,850 rectal cancer tumors (RT) included 4,550 (7.9%) RC. Comparing RC and SIC, RC presented at a younger age (56.2 vs. 64.5 years, p<0.001). RC were more common among women (50.6 vs. 47.0%, p<0.001). The ethnic distribution of SIC and RC were significantly different. SIC were more common among Whites (W) (76.0 vs. 51.0%, p<0.001). RC were more common among each ethnic minority group: Blacks (B) (19.9 vs. 14.3%), Hispanics (H) (13.0 vs. 6.5%), Asians (A) (14.9 vs. 2.7%), and American Indians/Alaskans (AI) (1.1 vs. 0.4%); p<0.001. RC were more common than SIC among women for every ethnic group (percentage of patients who are women: W 48.1 vs. 46.8%, B 59.3 vs. 50.6%, H 50.3 vs. 44.3%, A 46.5 vs. 41.1%, AI 72.0 vs. 47.1%), although this reached significance in only Black females (p=0.001). Mean survival was better in RC (93.4 vs. 65.8 months, p<0.001) by Kaplan-Meir analysis. **Conclusions:** This study demonstrates that SIC and RC are epidemiologically distinct tumors with different presentations and outcomes. Minority groups and females are more likely to present with RC. In addition, RC have better prognosis. Further studies are needed to investigate potential biological differences between these two tumors.

Comparison of Small Intestinal to Rectal Carcinoids

Variable	Small Intestinal (n=4,731)	Rectal (n=4,550)	p-Value
Age, years	64.5	56.2	<0.001
Female	47.0%	50.6%	<0.001
White	76.0%	51.0%	<0.001
Black	14.3%	19.9%	<0.001
Hispanic	6.5%	13.0%	<0.001
Asian	2.7%	14.9%	<0.001
American Indian/Alaskan	0.4%	1.1%	<0.001
White Females	46.8%	48.1%	0.313
Black Females	50.6%	59.3%	0.001
Hispanic Females	44.3%	50.3%	0.090
Asian Females	41.1%	46.5%	0.254
American Indian/Alaskan Females	47.1%	72.0%	0.061
Mean Survival, months	65.8	93.4	<0.001

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How Safe is Robotic Thyroidectomy via a Gasless Approach? A Meta-analysis of Current Literature N.R. Jackson,[1]* L. Yao,[2] E.H. Kandil.[1] *1. Tulane University School of Medicine, New Orleans, LA; 2. Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.*

INTRODUCTION The benefits afforded by robotics have lead to their increased use in surgery. The aim of the current study is to compare the efficacy of robotic thyroidectomy via a gasless, transaxillary approach with conventional cervical and endoscopic approaches. METHODS A systematic review was performed on publications in MEDLINE, EMBASE, the Cochrane Database of Systematic Review, and Web of Science indentified from the following keyword searches: robotic thyroidectomy or thyroid surgery, robot-assisted thyroidectomy or thyroid surgery. Clinical trials and observational studies in an adult population were included. Searches were limited to comparative articles of robotic thyroidectomy with conventional cervical and/or endoscopic thyroidectomy. Outcomes included operative time, length of hospital stay, and surgical outcome. Random effects models were used to pool estimates of the mean net difference or of the relative risk between outcomes on the two groups. RESULTS Eighty-four publications were indentified and only eight studies met inclusion criteria, totaling 2670 patients. Compared with open approaches, those who underwent robotic surgery reported greater cosmetic satisfaction, with a pooled net mean difference of -1.35 (95%CI: -1.69, -1.09). Robotic surgery is associated with a higher risk of transient hypocalcaemia compared with cervical and endoscopic techniques (RR = 2.37, 95%CI: 1.12, 5.02); however, heterogeneity is moderate (I2 = 59.4% and p = 0.06). CONCLUSION Our meta-analysis suggests that robotic thyroidectomy is at least as safe, feasible, and efficacious as conventional cervical and endoscopic thyroidectomy. Furthermore, robotic thyroidectomy shows superior cosmetic satisfaction among patients than conventional thyroidectomy. Additional studies, including cost-benefit analysis and larger controlled trials, are needed to further assess cost effectiveness, clinical outcomes and patient satisfaction of this procedure.

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Expectant Management of the Asymptomatic Primary is Safe in Patients undergoing Chemoembolization for Metastatic Neuroendocrine Carcinoma N.B. Jones,[1]* P. Tassone,[1] D.. Arrese,[2] D. Klemanski,[1] M. Shah,[1] C.R. Schmidt,[1] M. Bloomston.[1] *1. Surgical Oncology, Ohio State University, Columbus, OH; 2. Riverside Methodist Hospital, Columbus, OH.*

Background: Traditional dogma mandates resection of the primary lesion in metastatic neuroendocrine carcinoma (mNET), yet the fate of these lesions is unclear. We reviewed our experience with selective resection of primary tumors in patients with metastatic carcinoid undergoing transcatheter arterial chemoembolization (TACE). Methods: We reviewed 197 patients who underwent TACE for mNET. Indications for TACE were symptom palliation (diarrhea, flushing), hepatic progression, or extensive hepatic tumor burden. Primaries were left in situ if asymptomatic or if resection was considered high risk. Results: At the time of first TACE, 97 patients had undergone resection of their primary lesions. Of 100 primaries not resected pre-TACE, 93 were asymptomatic. During median follow-up of 35.6 months, 4 (4%) became symptomatic. An additional three primaries were resected post-TACE prior to symptoms developing. No deaths were related to primaries left in situ or operations involving their removal. Median overall survival (OS) is augmented to 41 months in patients who undergo resection of their primary tumor, regardless of pre- or post-TACE, as compared to 28 months for unresected primaries (p=0.016). However, when stratifying patients who underwent primary resection according to whether they were symptomatic or asymptomatic at time of resection, median OS post-TACE was 44 months versus 53 months, respectively (p=0.34) [Fig 1]. Patients with unresected asymptomatic primaries at time of TACE were more likely to be pancreatic in origin (p=0.015) and to have extrahepatic disease (p=0.025) as compared to those asymptomatic primaries removed pre-TACE. Conclusions: Asymptomatic primary tumors in patients with mNET uncommonly require intervention, and even more rarely become symptomatic after treatment of their metastases with TACE. Improved survival observed when the primary had been removed reflects selection bias rather than therapeutic benefit as waiting for primaries to become symptomatic did not affect outcomes. These data support the expectant management of an asymptomatic primary tumor in patients undergoing TACE for mNET.

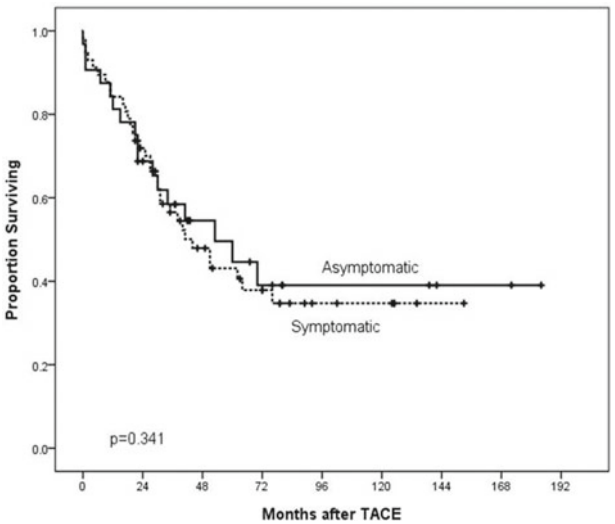

Figure 1. Overall survival after TACE for patients undergoing surgical resection of primary tumor based upon the presence of symptoms.

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Phase 2 Trial Results for Sunitinib and Transarterial Chemoembolization (TACE) in Inoperable Hepatocellular Carcinoma (HCC) Y.V. Wu,* G.M. Tomaszewski, G.J. Fetterly, B. Kuvshinoff, A. Groman, N.W. Wilkinson, N.I. Khushalani, R.V. Iyer. *Roswell Park Cancer Institute, Buffalo, NY.*

INTRO: TACE and oral anti-angiogenic agents have individually been effective for inoperable HCC. This is the first phase 2 trial evaluating the combination of sunitinib and TACE on HCC progression free survival (PFS) and overall survival (OS) METHODS: Eligibility included pts with ECOG PS of 0-1, inoperable HCC, Child Pugh class A-B, plts >100K, bilirubin <2, and were eligible for TACE. Treatment plan: Cycle 1: Sunitinib 37.5mg PO Daily D1-7 TACE w/ doxorubicin in lipodiol D8 Sunitinib 37.5mg PO Daily D15-36 2 wks of rest Subsequent Cycles: Sunitinib 50mg PO Daily 4 wks(escalation as tolerated) 2 wks of rest DCE-MRI, sVEGFr levels, monocytes counts, and sunitinib PK were assessed at D0, D8, D10, and D36. RESULTS: The median follow up was 12.8 months with 5 pts still alive. The median number of cycles given was 3 (range 1-7). The median PFS was 8 months (95% CI 4.3-9.3) and OS of 14.9 months (95% CI 6.3-27.1). 2 pts showed PR, 11 SD, and 3 with progression by RECIST criteria (total benefit 81%). Sunitinib steady state ranged from 20-150ng/ml which is above the IC50 for VEGF inhibition (4-30ng/ml). The median Ktrans change was -20% on D8 (sunitinib alone) and -27% on D36 (sunitinib+TACE). PK/PD modeling estimated sunitinib IC50 values of 15 and 10ng/ml for modulation of Ktrans and AUC90 respectively. The amount of viable tumor was 3% D8, 15% D36. sVEGFR2 changed with Ktrans and AUC90 changes. Monocyte counts decreased by 50% on D36. Eleven pts (69%) had grade 3/4 sunitinib toxicity. Of a total of 57 events, the most frequent were thrombocytopenia (10), amylase/lipase increase (9), lymphopenia (7), and fatigue (6). Dose delays and dose reductions occurred in 13 and 3 pts respectively. Reasons for discontinuing therapy were toxicity (7), progression of disease (7), and withdrawal of consent (2). CONCLUSION: This is the first phase 2 study combining sunitinib and TACE in the treatment of HCC. It increases PFS and OS with acceptable toxicities compared to current treatments. It also shows a relationship between sunitinib concentration and Ktrans, AUC90, sVEGFR2, and monocytes.

Patient Characteristics

Total	16 Patients
Age (Median)	74 (40-86)
Gender	
Male	12
Female	4
Child Pugh Class A	100%
Cirrhosis Etiology	
Hepatitis B	2
Hepatitis C	6
Alcohol	1
Unknown	7
ECOG Performance Score	
0	12
1	4
Extent of Disease	
Liver Only	10
Extrahepatic Disease	6

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A Phase I Trial of Isolated Hepatic Perfusion (IHP) using 5-FU and Oxaliplatin in Patients with Unresectable Isolated Liver Metastases (ILM) from Colorectal Cancer (CRC) D. Magge,* A. Zureikat, D. Bartlett, M. Holtzman, H. Choudry, J. Beumer, J.L. Holleran, S. Strychor, J. Pingpank, H.J. Zeh. *General Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: IHP is a proven approach for regional delivery of chemotherapy in patients with unresectable metastatic liver lesions. This study sought to determine the safety and MTD of administering 5FU in combination with fixed dose oxaliplatin via IHP. Methods:Prospective Phase I dose escalation with standard 3x3 dosing. Subjects with unresectable ILM from CRC scheduled to receive an HAI pump were eligible. IHP employed fixed dose oxaliplatin (previously established) with escalating doses of 5FU. 1^{o} endpoint was to determine MTD of this combination. 2^{o} endpoints were response to IHP alone (RECIST), PFS, and OS for the combination of IHP + HAI-FUDR. Systemic and IHP plasma PK of 5FU, its anabolites, total, and free platinum were determined by validated assays. Results:Between Aug 2007 - Mar 2011, 11 subjects were enrolled. All patients received at least one line of pre-IHP systemic chemotherapy. There were 4 Grade 3 SAE (36.3%) and no grade 4 events (table 1). 2 DLTs occurred in the second dose cohort of 300mg/m2 (see table 1). Dose escalation was therefore terminated and 200mg/m2 5FU was determined to be the MTD. There was 1 DLT in the dose de-escalating phase of 200mg/m2. At first follow-up, 9 pts (82%) demonstrated a partial response, while 2 (18%) exhibited stable disease. 64% of pts demonstrated a >50% decrease in CEA level. Actuarial 1 and 2 year survival was 100% and 75% respectively, with median follow-up of 23 mos. IHP exposures (AUC0-60min) were 10.9±4.5 μgPt h/mL (free platinum), 49.3±30.7 μg h/mL 5FU (DL1) and 70.5±35.5 μg h/mL 5FU (DL2). Free platinum represented 82±14% of total platinum. Systemic exposure (AUC0-inf) relative to IHP exposure was negligible for both total platinum (1.1±1.5%) and 5FU (0.09±0.10%). IHP exposure to metabolites relative to 5FU was 4.9±2.5% for FUrd and 0.23±0.14% for FdUrd, respectively. Conclusions: MTD for IHP with 5FU and oxaliplatin is 200 mg/m2 and 40mg/m2 respectively. Systemic exposure to the agents was minimal during IHP. The response and survival observed in this dose escalation study warrants assessment in a larger phase II trial.

Table 1

Patient #	5FU Dose (mg/m^2)	Oxaliplatin dose (mg/m^2)	DLT	SAE (grade 3)	Response
1	200	40	No	No	PR
2	200	40	No	No	PR
3	200	40	No	No	PR
4	300	40	No	No	PR
5	300	40	Yes	Yes - hyperbilirubinemia, hemorrhage	PR
6	300	40	No	No	SD
7	300	40	No	Yes - pleural effusion	PR
8	300	40	No	No	PR
9	300	40	Yes	Yes - hematoma, ascites	PR
10	200	40	Yes	Yes -Thrombocytopenia, hemorrhage, pleural effusion	SD
11	200	40	No	No	PR

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Impact of Treatment Modality and Number of Lesions on Recurrence and Survival Outcomes after Treatment of Colorectal Cancer Liver Metastases A. Saxena,* T.C. Chua, F.C. Chu, K. Ng, P. Herle, A. Sarkar, J. Zhao, D.L. Morris. *Surgery, St George Hospital, Kogarah, NSW, Australia.*

Background Hepatic resection (HR) is an effective treatment for colorectal cancer liver metastases (CRCLM). Ablative strategies have been used to both facilitate treatment in patients with otherwise unresectable tumors and as a isolated treatment option for limited CRCLM. We evaluated the efficacy of HR, concomitant HR and ablation and isolated ablation on recurrence and survival outcomes after treatment of CRCLM in patients with 1-4 and ≥ 5 lesions, respectively. Methods A retrospective review of a prospectively collected hepatobiliary surgery database was performed on patients who underwent treatment for CRCLM between 1990 and 2010. Patients with extra-hepatic disease were excluded. Pre-operative and treatment characteristics were compared between patients who underwent HR, concomitant HR and ablation and ablation alone. The impact of treatment modality on survival and recurrence outcomes was determined. Results Of the 701 patients who met inclusion criteria, 550 had 1-4 lesions and 151 had ≥5 lesions. Overall median survival for the entire cohort was 35 months with 5- and 10- year survival of 33% and 20%, respectively. Overall median and 5-year recurrence-free survival (RFS) was 13 months and 21%, respectively. For patients with 1-4 lesions, median survival was 37 months with 5-year survival of 36% (Figure 1). Stratified by procedure type, 5-year survival was 41% in patients who underwent HR, 35% in patients who underwent concomitant HR and ablation and 13% in patients who underwent ablation alone (p<0.001). For patients with ≥5 lesions, median survival was 28 months with 5-year survival of 23%. There was no significant difference in overall survival between the three treatment groups (p=0.078). Conclusion HR is the gold standard treatment in patients with 1-4 lesions. When ≥ 5 lesions are present, ablative strategies are useful, particularly when they facilitate hepatic intervention in otherwise unresectable patients.

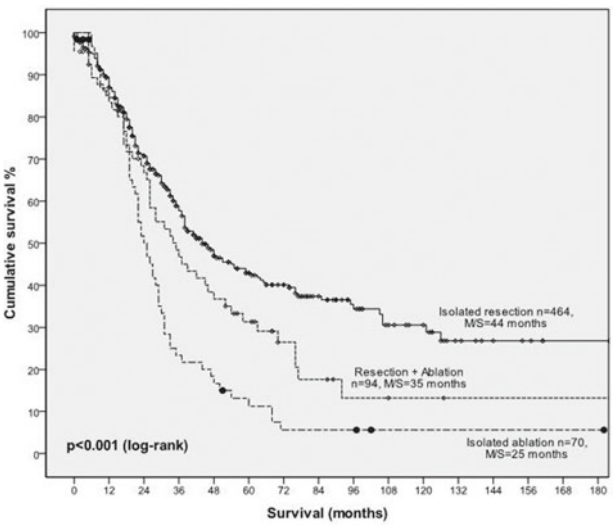

Figure . Overall survival of patients with 1-4 lesions after hepatic intervention for colorectal cancer liver metastases, stratified by treatment modality (p<0.001).

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The Use of Endoscopic Ultrasound in Staging Pancreatic Cancer: An Exercise in Futility? G.B. Deutsch,* S. Anantha Sathyanarayana, M. Beg, J.L. Ricci, J.D. Sullivan, J. Wang, C.C. Conte. *North Shore University Hospital, Hofstra-NSLIJ School of Medicine, Manhasset, NY.*

Introduction Over the last few decades, outcomes in pancreatic cancer have barely changed despite the advancement in diagnostic modalities. Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) has been utilized to better evaluate local invasion and the involvement of surrounding nodal basins, as well as sample tissue for pathologic diagnosis. Despite several

reports defending the accuracy of EUS for establishing resectability, its utility in determining tumor stage is a matter of debate. Methods A retrospective review was performed of 47 subjects with a diagnosis of pancreatic cancer determined to be resectable. All patients underwent surgical resection between January 2009 and March 2011 at a major tertiary care hospital. Patient demographic information was extracted from the institutional tumor registry, while EUS and pathology results were collected from patient charts. Subjects were excluded if they received neoadjuvant chemoradiation and/or had a delay of three or more months between EUS and definitive surgical resection. Results The average age of our study sample at diagnosis was 69.7 (range 33-87), with women accounting for 55.3% of cases. The pancreatic tumors were anatomically located as follows: 57% head, 23% tail, 10% neck/body, and 10% body/tail. Adenocarcinomas accounted for 81% of cases, whereas endocrine tumors and intraductal papillary mucinous neoplasms (IPMN) were 10% and 9%, respectively. The preoperative EUS staging concurred with final pathologic stage in 29.8%, was greater than surgical stage in 12.8%, and less than pathologic stage in 55.3%. The accuracy of EUS for T staging was 34.0% and for N staging was 63.8%. Patients were found to have lymph node involvement on final pathology in 31.9% of cases where preoperative EUS reported no lymphadenopathy. Conclusions Although EUS is reliable in diagnosing unresectable pancreatic cancer, it seems to lack the precision to adequately stage locoregional disease. Using only EUS for preoperative staging may fail to identify potential candidates for neoadjuvant chemoradiation.

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Low 18F-fluorodeoxyglucose Uptake on Positron Emission Tomography is a Positive Prognostic Factor for Stage I and II Pancreatic Cancer J.M. Pimiento,[1]* H. Boutrid,[1] J. Weber,[1] J.M. Farma,[2] R.D. Kim,[1] D. Chen,[1] S. Razzaque,[1] S.E. Hoffe,[1] J. Klapman,[1] P.J. Hodul,[1] M.D. Chuong,[1] J. Park,[1] R. Shridhar,[1] G.M. Springett,[1] K. Almhanna,[1] E.A. Eikman,[1] R. Karl,[1] M.P. Malafa.[1] *1. Surgical Oncology, H Lee Moffitt Cancer Center, Tampa, FL; 2. Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Metabolic activity as defined by the uptake of 18F-fluorodeoxyglucose (FDG) on Positron Emission Tomography (PET) has proven beneficial as a prognostic marker for multiple malignancies; however, no study has examined the prognostic value of PET in stage I and II pancreatic cancer. We examined the value of PET FDG uptake in early pancreatic cancer. Methods: Using a comprehensive pancreatic adenocarcinoma database, we identified patients with early stage pancreatic cancer (I-II) who underwent pancreatectomy for cancer and had PET scan performed as part of their preoperative evaluation from 2004 to 2010. Patients were divided by the median primary tumor standard uptake value (SUVmax) into two groups: high and low FDG uptake. The primary outcomes were overall survival (OS) and disease free survival (DFS). Kaplan-Meier estimate was used for survival analysis. Pathologic data were compared using Fisher's exact and chi-square. Results: We identified 105 patients with resected stage I and II pancreatic cancer who had PET scans as part of their preoperative evaluation. 51 patients had low FDG uptake while 54 patients had high FDG uptake. The median age at diagnosis was 69 (24-89) years, 57% of the patients were male. 84 (81%) patients had PET avid tumors, while 20 (19%) patients did not. The median SUVmax was 5.1. High FDG uptake correlated with pathologic stage (p=0.012). Median follow-up was 12.3 (0-56) months. Patients with low FDG uptake had a significantly better median OS than patients with high FDG uptake (27 vs. 16 months; p=0.036). Recurrence occurred in 64 (60%) patients. Patients with low FDG uptake had significantly longer median DFS than patients with high FDG uptake (14 vs. 12 months; p=0.049). Conclusion: Low 18F-fluorodeoxyglucose uptake in PET scans for stage I and II pancreatic cancer correlates with improved overall survival and disease free survival. This observation supports the concept that glucose metabolic pathways are important in pancreatic cancer biology, and that PET scan activity can be used as a prognostic biomarker after pancreatectomy for pancreatic cancer.

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Transfusion of Irradiated Autologous Blood for Surgical Resection of Hepatobiliary Pancreatic Cancers L. Ruo,* C. Barnett, S. Orr, F. Farrokhyar, J.J. Hankinson. *McMaster University, Hamilton, ON, Canada.*

Major oncologic resections for hepatobiliary/pancreas (HBP) malignancies often result in significant blood loss and frequently require perioperative blood transfusion. Autologous blood transfusion (ABT) eliminates the possibility of infecting the recipient with blood-borne viral diseases; prevents alloimmunization; and may avoid potential short and long term consequences of homologous blood transfusion (HBT). Irradiation of salvaged intraoperative blood for ABT may be feasible and obviate the need for allogeneic blood in these patients. METHODS: Patients from a single institution who underwent elective HBP oncologic resections were included in our analysis. Our historic cohort (HC) underwent resection from Jan/05 to May/08 and received only HBT. Patients were enrolled in a prospective cohort study and underwent resection between Nov/07 and Feb/11; they preferentially received irradiated salvaged intraoperative blood, but also received HBT if indicated. Clinical, operative, tumour, and treatment related data was collected, along with transfusion requirements. The rate of HBT and the frequency of associated complications were compared. Factors associated with blood transfusion were analyzed in both groups. RESULTS: 253 patients comprised our HC and 32 patients participated in the intraoperative blood conservation (IBC) study. Of 285 patients, 159 (56%) received HBT (31% IBC, 59% HC, p=0.004). The ABT rate in the IBC cohort was 25% reducing the requirement for HBT by 44%. For either HC or IBC patients who received any blood transfusion, there was no significant difference in the rate of postoperative infections, a complication associated with HBT (37% overall, 28% IBC, 38% HC). IBC patients receiving ABT had an infection rate of 25% vs 30% for those receiving any HBT. On multivariable logistic regression analysis, significant factors for blood transfusion were estimated blood loss, gender, preoperative anemia, and ASA class. CONCLUSION: Transfusion of irradiated autologous blood for major HPB oncologic resections appears feasible and reduces the need for HBT. Evaluation of blood conservation strategies should be rigorously studied in high-risk patients.

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Risk of Occult Irresectable Disease at Liver Resection for Hepatic Colorectal Metastases: A Contemporary Analysis K.A. Bickenbach,[1]* R.P. DeMatteo,[2] Y. Fong,[2] P. Kingham,[2] P.J. Allen,[2] W.R. Jarnagin,[2] M.I. D'Angelica.[2] *1. Surgery, University of Medicine and Dentistry of New Jersey, Newark, NJ; 2. Memorial Sloan-Kettering Cancer Center, New York, NY.*

INTRODUCTION: Complete resection is the most effective therapy for patients with colorectal liver metastases (CRLM). Traditionally, rates of irresectable disease at laparotomy ranged from 15%-21%. Diagnostic laparoscopy has previously been shown to be an effective method of preventing non-therapeutic laparotomy in selected patients. The aim of this study was to analyze the resectability rate and role of diagnostic laparoscopy in a contemporary cohort. METHODS: Using a prospectively maintained database we identified patients that were explored for resectable CRLM. Preoperative work-up included CT of the chest, abdomen and pelvis and colonoscopy. Further imaging was performed at the discretion of the treating physician. Clinical and pathologic data associated with the finding of irresectable disease were analyzed. RESULTS: From 2008-2010, 455 patients were explored. The operative intent was changed in 46 patients (10%). Of these, the operation was aborted in 20 patients (4%) due to irresectable disease, 9 (2%) underwent ablation instead of resection, 15 (3%) had hepatic artery infusion pumps (HAIP) placed instead of resection, and 2 (0.4%) underwent the first of a planned 2-stage resection. Of the 20 patients with irresectable disease, 4 (20%) had additional liver disease, 5 (25%) had extrahepatic nodal disease, and 11 (55%) had peritoneal carcinomatosis. The only factor associated with irresectable disease was a prior history of extrahepatic disease, which was present in 40% of those found irresectable versus 13% of those resected (p=0.004). There was no difference in the number or type of preoperative radiologic tests. Diagnostic laparoscopy was performed in 55 patients. Four of these patients had irresectable disease, and 3 were spared an unnecessary laparotomy. Therefore, the yield of diagnostic laparoscopy was 5% and the sensitivity 75%. CONCLUSIONS: The finding of irresectable disease for radiologically resectable CRLM is a rare event with modern radiologic assessment. Diagnostic laparoscopy has a low yield and should only be considered if there is a history of extrahepatic disease or suspicious findings on preoperative imaging.

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Significance of CEACAM6 Expression in Cholangiocarcinoma
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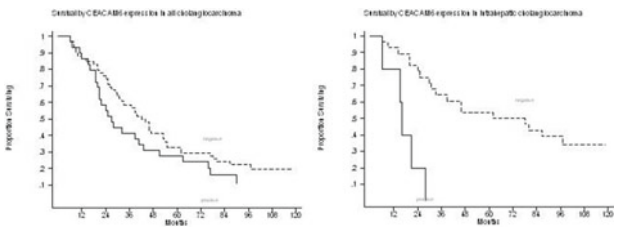
Background: The entire biliary tree is at risk for malignant change, but little is known about differences in molecular pathogenesis with respect to anatomic site. CEACAM6 is a membrane protein involved in cell adhesion and signaling that is overexpressed in pancreatic adenocarcinoma and associated with poor prognosis. This study examines CEACAM6 expression in the entire spectrum of cholangiocarcinoma and its relationship to outcome. Methods: Tissue microarrays containing triplicate cores of paraffin-embedded surgical specimens from patients with cholangiocarcinoma (hilar, intrahepatic, distal) and control tissue were probed for CEACAM6 by immunohistochemistry. Clinical, pathologic and survival data were analyzed and correlated with CEACAM6 expression. Survival was estimated using the Kaplan-Meier method and compared with log rank test. Results: One hundred twenty cases of cholangiocarcinoma from 1992-2007 were assembled in the tissue microarrays. Strong CEACAM6 signal was present in 30/60 (50%) of hilar tumors, 7/45 (16%) of intrahepatic tumors, 7/15 (47%) of distal tumors, and none of the control tissues. Overall median survival and follow-up were 36.4 months and 98.2 months, respectively. CEACAM6 staining did not correlate with sex, grade of differentiation, positive lymph nodes, vascular invasion or metastases but was associated with age > 65 ($p<0.05$) and higher T stage ($p<0.05$). After R0 resection, CEACAM6 expression was associated with disease-specific survival (DSS) only in the subset of patients with intrahepatic cholangiocarcinoma (median DSS 78 months for negative and 16 months for positive, $p<0.002$)(See Figure). Vascular invasion was the sole independent predictor of survival on multivariate proportional hazards regression (HR=1.765 [1.148-2.714 95%CI], $p<0.009$) in the entire cohort. Conclusions: CEACAM6 may serve as a marker of poor outcome in patients with intrahepatic cholangiocarcinoma and should be further evaluated as a means of selecting patients for adjuvant therapy after resection.



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Are We Justified in Excluding Patients with Combined Hepatocellular-Cholangiocarcinoma from Transplantation? R.T. Groeschl,* S.G. Pappas, K.K. Christians, S. Tsai, E.J. Quebbeman, T.C. Gamblin, K.K. Turaga. *Medical College of Wisconsin, Milwaukee, WI.*

BACKGROUND: Although transplantation has shown remarkable survival benefit for patients with hepatocellular carcinoma (HCC), there is limited data to support or refute the treatment of combined hepatocellular-cholangiocarcinoma (cHCC-CC) with transplantation. We hypothesized that patients with mixed histology had a lower overall survival than HCC after liver transplantation. METHODS: Patients with localized HCC and cHCC-CC treated with surgical resection (SR) or transplant (TP) were identified using the Surveillance, Epidemiology, and End Results (SEER) Database (1973-2007). Survival was analyzed using the Kaplan-Meier model. Prognostic factors were examined with Cox regression analyses. RESULTS: We identified 3378 (1447 [43%] TP and 1931 [57%] SR) patients with HCC, and 54 (19 [35%] TP and 35 [65%] SR) patients with cHCC-CC. Cohorts were similar with respect to age, gender, race, and tumor size. Median overall survival (OS) was 68 months (95% confidence interval (CI): 64-75) for HCC and 36 months (95% CI: 19-89) months for cHCC-CC ($p = 0.01$). Patients undergoing SR of HCC and cHCC-CC had similar 3-year OS (55% vs. 46%, $p=0.4$). Overall 3-year survival of patients undergoing TP was significantly longer for HCC (78%) than for cHCC-CC (48%, $p=0.01$). After adjusting for age at diagnosis and gender, multivariate modeling revealed an increased hazard ratio for patients undergoing TP with a mixed histology: HR 2.5 (95% CI: 1.2-5.1, $p=0.01$). CONCLUSIONS: Patients undergoing transplantation with localized cHCC-CC have a shorter overall survival than patients with HCC. In an era of organ shortage, this may justify excluding patients with cHCC-CC from transplantation. Our data is limited by the lack of tumor and host-specific factors, and prospective validation of this conclusion is warranted.

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Resection and Laparoscopic Radiofrequency Thermal Ablation of Solitary Colorectal Liver Metastasis O. Agcaoglu, S. Aliyev, F. Aucejo, A. Siperstein, E. Berber.* *Cleveland Clinic, Cleveland, OH.*

Background: There has been significant interest regarding the outcome of patients with solitary colorectal liver metastasis (CLM) undergoing RFA. We previously reported on the initial results of RFA and resection for such patients. The aim of this study is to provide an update on our series and see if a subgroup of similar patients could be identified for comparison. Methods: Between 2000-2011, 117 patients underwent liver resection and 99 patients laparoscopic RFA for solitary CLM. Patients were evaluated in a multidisciplinary fashion. Data were collected from a prospectively maintained IRB approved database. Analyses were performed using Student t, Chi-Square, and Kaplan Meier Survival tests. Results: The groups were similar for age, gender, and chemotherapy exposure. Tumor size was 4.1 ± 0.2 cm vs 3.4 ± 0.2 cm for resection and RFA groups, respectively, $p=0.017$.RFA patients tended to have a higher ASA score and incidence of cardiopulmonary comorbidities and extra-hepatic disease (EHD) at time of treatment. Indications for RFA included technical reasons (n=12), patient comorbidities (n=39), EHD (n=27), and patient decision (n=21).The complication rate was 22% (n=24) for resection and 2% (n=2) for RFA. The local recurrence rate at the site of resection and RFA was 14% and 31%, respectively. The overall Kaplan-Meier 5-year actual survival was 49% for resection and 21% for RFA, $p=0.001$.Median disease-free survival was 34 months for resection and 14 months for RFA, $p<0.001$.For patients with tumor size <3 cm and without EHD, the 5-year actual overall survival was 56% for resection and 35% for RFA patients ($p=0.370$). For the resection vs RFA patients, the cause of death was due to progression of hepatic metastases in 31% and 23%; EHD in 42% and 43%; both hepatic and EHD in 15% and 11%; and unrelated non-cancerous events in 12% and 23% of the patients, respectively. Conclusions: In this study, although patients in both groups had a solitary CLM, medical comorbidities and EHD were different, prompting selection of therapy. Based on our results, we can not recommend RFA for resectable solitary CLM and this question needs to be answered in a randomized study.

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Post-operative CEA Trends Correlate with Survival and Patterns of Recurrence after Hepatectomy for Colorectal Cancer Metastases L.A. Shirley,* M. McNally, J. Huntington, N. Jones, L. Malhotra, M. Bloomston, C. Schmidt. *The Ohio State University Medical Center, Columbus, OH.*

Background: Pre-operative carcinoembryonic antigen (CEA) level is associated with outcome after hepatectomy for colorectal cancer metastases. In this study we sought to determine the relationship between post-operative CEA and outcome after hepatectomy. Methods: A single institution retrospective review of hospital records from 1993 to 2010 found 339 patients who underwent a liver resection for CRC metastases. Of these, 140 had CEA levels drawn preoperatively, post-operatively, and at least once more in follow-up. A ΔCEA level was calculated by subtracting the initial post-operative CEA level from the highest CEA level drawn in follow-up. Outcomes were compared between patients with ΔCEA less than 5 and greater than 5. Results: Of 140 patients, 61 had ΔCEA less than 5 and 79 had ΔCEA greater than 5. Patients with low ΔCEA had improved median overall survival (OS) (70.2 months) compared to those with high ΔCEA (38.7 months, $P=0.0001$). However, there was no significant difference in progression-free survival (PFS) (13.0 months vs. 12.3 months, $P=0.982$). 100 patients had recurrence after hepatectomy, 69 with high ΔCEA and 31 with low ΔCEA. Patients with low ΔCEA were more likely to have a single site of recurrence (77.4% vs. 53.6%, $P<0.0001$) and there were other distinct patterns of recurrence between the two groups (Table 1). Conclusions: Although a rising CEA after hepatectomy for CRC metastases is associated with worse overall survival, there is no difference in progression-free survival between patients with rising CEA and those with stable-to-decreasing CEA. Patients with stable-to-decreasing CEA have patterns of recurrence more amenable to locoregional therapy. Post-operative CEA values are an

important component of oncologic surveillance, and patterns of rise and fall may indicate patterns of recurrence.

Patterns of recurrence based on CEA trend

	Low ΔCEA	High ΔCEA	P value
Single Site Recurrence	77.4%	53.6%	<0.0001
Multifocal Recurrence	22.6%	46.4%	<0.0001
Liver Only Recurrence	45.2%	36.2%	0.252
Lung Only Recurrence	16.1%	5.8%	0.457
Pelvis Only Recurrence	12.9%	8.7%	0.813
Further Locoregional Therapies Performed	54.8%	47.8%	0.086

Comparison of patients with low ΔCEA vs. patients with high ΔCEA after hepatectomy in terms of patterns of recurrence and if any further locoregional therapies were performed beyond the hepatectomy.

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Early Experience with Robotic Radiosurgery for Local Control of Liver Metastasis M.E. Kwiatt,* T.A. LaCouture, F.R. Spitz. *Cooper University Hospital, Camden, NJ.*

Liver toxicity limits radiation therapy for liver metastasis; however, robotic radiosurgery delivers effective doses with limited toxicities. Robotic radiosurgery may be an effective treatment for liver metastases in patients with lesions not amenable to surgical resection. We conducted a retrospective study of patients treated with robotic radiosurgery for liver metastasis at our institution from June 2008 and June 2010. Medical records were reviewed and all cases discussed in multi-disciplinary conference. Pre-radiosurgery and follow-up abdominal computed tomography (CT) scans reviewed for treatment response. Our primary endpoint was local recurrence, defined as increased enhancement or tumor progression within the treatment field on follow-up CT scan. Thirty-three patients had 37 liver metastasis treated with robotic radiosurgery (17 colorectal, 4 ovarian, 4 breast, 3 melanoma, 2 liver, 2 lung, 1 gastric, 1 cholangiocarcinoma, 1 pancreas, 1 anal, 1 bladder). Eighteen of 33 patients (54.5%) had isolated liver metastasis. Prior to radiosurgery 27 of 33 patients (81.8%) had undergone surgical resection of primary tumor, 26 of 33 patients (78.8%) were treated with chemotherapy for metastatic disease, and 15 of 33 patients (45.5%) had non-liver radiation therapy. Median time from primary diagnosis to radiosurgery treatment was 33.3 months (5.7 to 320 months). Patients received median radiation dose of 30 Gy (22.5 to 42) over 3 to 5 fractions. Median follow up was 8.1 months (1.2 to 23.5). There were no cases of liver failure. Sixteen patients had disease progression outside the treatment field (15 liver, 6 systemic) with a median time to progression of 4.6 months (0.9 to 17.6). Five lesions (13.5%) had in field progression with a median time to progression of 10 months (2.6 to 13.1). Seventeen patients (51.5%) died during follow-up. Robotic radiosurgery offers a potential local therapy for patients with metastatic liver disease with limited toxicity. Longer follow-up and more patients are required to better assess its safety. Robotic radiosurgery may fill a role for patients with lesions not amenable to traditional ablative and surgical techniques.

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WITHDRAWN

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Age-related Outcomes following Hepatectomy and Liver Ablation: An Analysis of 8,734 Patients from the National Inpatient Sample (2004 – 2008) R. Tran, S. Patil,* C. Ronald. *Surgery, Saint Barnabas Medical Center, Livingston, NJ.*

Introduction: Both primary and secondary liver cancers are associated with a poor prognosis. Although the primary treatment is systemic chemotherapy, an increasing number of patients are candidates for surgical or ablative liver-directed therapy. This study aimed to evaluate age-related trends, complication risks, and the morbidity and mortality following surgical or ablative treatment of primary and secondary liver cancers in a large cohort of patients in order to allow more precise pre-operative surgical risk stratification. Materials and Methods: Discharge data on 40,276,240 patients from the Nationwide Inpatient Sample (NIS) database (2004-2008) was analyzed. Data on patients undergoing hepatic lobectomy (HL), partial hepatectomy (PH), and/or liver ablation (LA) as the primary procedure was abstracted including age, gender, elective status, co-morbidities, length of stay (LOS), complications, and mortality. Nine age groups in increments of 10 years were formed. Categorical and continuous variables were compared using Chi-square and Student's t test. Results: 8,734 patients meeting the inclusion were identified from the NIS. 3079 underwent HL, 5036 underwent PH, and 619 underwent LA. Male to female ratio was 1:1. Hepatic metastases was the most common primary diagnosis for HL(44%), PH(46%), and LA(49%). Mortality rates were 4.4, 2.8, and 1.3% respectively and were highest in patients aged 81-90 years (9.5, 8.1, and 2.9%). Non-elective mortality rates were higher compared to elective in the HL (11.5 vs. 3.4%) and PH (8.6 vs. 1.9%) groups, but lower in the HA (0.9 vs. 1.4%) group. Overall, HL had the highest mean LOS of 8.9 days, compared to PH (7.8 days) and LA (4.6 days). Conclusions: HL and LA are performed most commonly for hepatic metastases (46%). Liver directed therapies were utilized most commonly in patients age 51-70 years (49%), and much less commonly with advancing age, perhaps as a consequence of decreased performance status. Hepatic resection is associated with increased mortality with advancing age, mortality is higher with more complicated resection and lowest with LA alone.

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The Successful Implementation of Irreversible Electroporation for Tissue Ablation in Primary and Secondary Tumors of the Liver and Pancreas G.B. Deutsch,* S. Anantha Sathyanarayana, H. Walden, M. Beg, C.C. Conte, J.D. Sullivan, J. Wang. *North Shore University Hospital, Hofstra-NSLIJ School of Medicine, Manhasset, NY.*

Introduction Irreversible electroporation (IRE) is a novel modality that allows for tissue ablation by delivering nanosecond electrical waves and creating microscopic defects in the cell membrane. The lack of thermal damage and decreased procedure time with IRE is a major advantage over existing therapies for ablation. Despite major advances and increased availability, there have been relatively few published experiences amongst surgical oncologists. We present our early results with this new technology. Methods A retrospective review was performed of nine cases during which IRE was employed for soft tissue ablation. All patients underwent IRE by a single surgical oncologic group at a major tertiary care institution between February 2011 and August 2011. Indication for surgery, tumor size and location, total time per IRE treatment, number of electrodes and spacing, and margins were collected for each patient. Cases were evaluated for intraoperative and postoperative complications. Results The average age of our patients was 60.7 years. Six patients were males and three were females. The median length of stay was 10 days (7.0-27.0: mean 12.5). Seven of the subjects had liver metastases secondary to colon (3), breast (2), small intestinal (2) cancer; one patient had a primary pancreatic neuroendocrine malignancy; one patient had primary hepatocellular carcinoma. Tumors were singular in five patients and multiple in four. All nine patients had IRE performed with the primary goal of ensuring negative microscopic margins. Negative margins were confirmed in seven patients. Total time per IRE treatment was 5.21 minutes with a mean 4.25 treatments per patient. Only one patient sustained an intraoperative complication (new onset atrial fibrillation), which was treated medically, and resolved before discharge. No mortalities were recorded at 30 days. Conclusions IRE is a feasible and safe modality for helping to ensure negative margins after liver and pancreatic resection. Further larger scale, prospective randomized trials are needed to confirm our findings and make conclusions about mortality benefit.

IRE patient data

Patient	Age	Sex	ASA class	Primary cancer	Mets	Number of masses	Segment	Maximum tumor dimension (cm)	Procedure	Time per treatment (min)	Number of electrodes	Maximum Electrode Spacing (cm)	Intraoperative/ Postoperative Complications
1	62	M	3	Colon	Liver	One	8	1.7	RFA, IRE	16.30	4	2.8	New onset atrial fibrillation
2	71	F	4	Breast	Liver	One	3 and 4	5.5	RFA, IRE	3.66	2	2.0	None
3	70	F	3	Breast	Liver	Multiple	6 and 7	5.1	RFA, IRE	3.75	2	2.0	None
4	50	M	3	Small Intestine	Liver	One	7 and 8	2.7	RFA, IRE	2.28	4	2.6	None
5	75	M	3	Colon	Liver	Multiple	Diffuse	1.3	IRE	4.27	2	1.5	None
6	50	M	2	Colon	Liver	Multiple	Diffuse	5.5	IRE	5.11	4	2.0	None
7	60	M	3	Pancreas	None	One	n/a	1.1	IRE	2.55	2	1.0	None
8	47	F	2	Small Intestine	Liver	Multiple	Diffuse	1.0	RFA, IRE	3.95	2	1.5	None
9	57	M	4	Liver (HCC)	None	One	3 and 4	9.5	IRE	4.91	2	2.0	None

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Revisiting the Prognostic Significance of Positive Peritoneal Cytology in Pancreatic Cancer K.T. Chen,* S. Singla, P. Papavasiliou, K. Devarajan, J.P. Hoffman. *Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Positive peritoneal cytology (PPC) in the setting of pancreatic cancer predicts a poor prognosis, such that it is considered metastatic disease in the American Joint Commission on Cancer staging guidelines. We reevaluate the role of PPC, with particular attention to outcomes following neoadjuvant therapy. Methods: We retrospectively identified 185 patients from January 1, 2000 to present with the diagnosis of pancreatic adenocarcinoma who had undergone peritoneal washings with cytology at the time of planned resection. Data regarding demographics, tumor stage, intraoperative cytology, surgical and chemoradiation therapeutics, and clinicopathological outcomes were analyzed, with the primary endpoints being disease-free and overall survival (DFS and OS). Results: 20 patients (11%) had PPC at the time of planned resection; of these, 11 patients (55%) received neoadjuvant therapy prior to surgery. 165 patients (89%) had negative peritoneal cytology (NPC) at the time of planned resection; of these, 75 (45%) received neoadjuvant therapy prior to surgery. All patients proceeded with resection in the absence of visible metastatic disease. 42% of NPC reached 2-year survival compared to just 20% of patients with PPC. Overall, patients with PPC vs. NPC had significantly poorer DFS ($p<0.0064$) and OS ($p<0.0135$). When stratifying by neoadjuvant therapy, in those patients with stage II disease or higher who did not receive neoadjuvant therapy, multivariable CART analysis revealed that PPC predicted poorer DFS compared with NPC ($p<0.004$). However, among stage II or higher disease receiving neoadjuvant therapy, it failed to show a significant difference in DFS or OS between PPC and NPC. Conclusion: Overall, patients with positive peritoneal cytology are shown to have worse DFS and OS compared to patients with negative peritoneal cytology in pancreatic adenocarcinoma. However, after multivariable analysis, the prognostic significance of positive peritoneal cytology disappears in those patients with stage II and higher disease receiving neoadjuvant therapy.

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Pancreaticoduodenectomies in High Volume Centers: Direct Transfer to Floor Improves Length of Stay without Affecting Morbidity or Mortality V. Siripurapu,* E. Liu, A. Khithani, D.R. Jeyarajah. *Dallas Methodist, Dallas, TX.*

Introduction: Pancreaticoduodenectomy (PD) is a complex procedure necessitating the highest level of co-ordinated care from preoperative considerations to the recovery period. The average cost for a patient staying in the ICU is higher than for standard telemetry. We intended to look at a series of PD patients who were directly sent to the telemetry floor instead of ICU, as part of a policy implementation over the years and analyze if there was any detriment to this economic utilization. Methods: A retrospective database of 622 patients over an eight year period from 2005-2011 who underwent pancreatic surgery was interrogated; performing surgeon, procedure type, preoperative diagnosis, patient co-morbidities and postoperative morbidity and mortality were isolated. A threshold of 40 pancreaticoduodenectomies per year was considered baseline for the year to be included in analysis. Results: 231 patients underwent a PD from 2006-2011. Three separate years were chosen having met PD threshold stipulated in our study; 2006 (41 pts), 2008 (42 pts), and 2010 (48 pts). There was equal distribution of patients with pancreatic cancer through the years ($p=0.96$). The mean age of the patients for the respective years, their gender, operative morbidity (cardiac event, wound infection, pancreatic leak, delayed gastric emptying, and GI bleed), and their mean co-morbidity index are shown in Table 1. 36% of patients were transferred to the floor in 2006, 52% in 2008 and 60% in 2010 ($p=0.01$). Mean length of stay decreased significantly from 2006 to 2010 ($p<0.05$). There were no operative mortalities in these years. Conclusion: With an equal volume of pancreticoduodentomies in analyzed years with similar age and patient co-morbidities, there was no increase in operative morbidity or mortality, but an improved length of stay by implementing direct transfer to floor in recent years. We recommend that this be standard in those centers with high volume pancreatic surgery.

Characteristics of patients undergoing pancreaticoduodenectomy under one surgeon

	2006 (N=41)	2008 (N=42)	2010 (N=48)	p value
Number of Patients	41 (31)	42 (32)	48 (37)	[NS] p=0.1949
Mean Age (yrs)	63.9±5.79	65.4±4.67	63.6±5.26	[NS] p>0.05
Gender				
Male	16 (39)	18 (43)	24 (50)	[NS] p=0.1492
Female	25 (61)	24 (57)	24 (50)	[NS] p=0.8508
Mean Co Morb Index	2.24±0.77	2.12±0.68	2.1±0.70	[NS] p>0.05
Operative Indication				
Pancreatic Cancer	26 (63)	21 (50)	21 (43)	[NS] p=0.9699
Mean Hospital LOS (days)	16±4.81	14±2.70	12±1.95	[S] p<0.05
Transfer to Floor	15 (36)	22 (52)	29 (60)	[S] p=0.0119
Morbidities Count Total	27 (13)	21 (10)	38 (15)	[NS] p=0.2743

Percentages in parentheses
[NS] no significant difference
[S] significant difference

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Does the "July Effect" Pertain to Hepatopancreaticobiliary Resection for Cancer? Answers from the Nationwide Inpatient Sample P.D. Colavita,* A.Y. Zemlyak, S. El Djouzi, A.L. Walters, A.E. Lincourt, D.A. Iannitti, B.T. Heniford. *General Surgery, Carolinas Medical Center, Charlotte, NC.*

Background: The purpose of this study is to use the Nationwide Inpatient Sample (NIS) to examine seasonal discrepancies based on the academic calendar for morbidity and mortality in teaching hospitals in the United States. Methods: Hepatopancreaticobiliary oncologic resections were examined using the Nationwide Inpatient Sample (NIS) data from 2005-2009 for all hepatic, pancreatic, and biliary cancer resections in patients having surgery in facilities identified as teaching hospitals. Outcomes (inpatient death, length of stay, disposition, and total charges) were compared at the beginning, middle, and end of the academic calendar: July/August (time 1, T1), January/February (T2), and May/June (T3). Results: A total of 9760 resections met inclusion criteria: 3366 in T1, 3213 in T2, and 3181 in T3. There was no significant difference in age, gender, race, or admission type (emergent, urgent, or routine). There were increased admissions as transfers from an outside hospital in T2 vs T1 and T3 (2.81% vs 1.68%, $p = 0.0220$). There was no significant difference in mortality rate ($p=0.3133$) or rate of routine discharge from the hospital. There was a small, yet significant, difference in length of stay for T1 vs T2 and T3 (10.8days vs 10.4days, $p = 0.0095$) and total charges for T1 vs T2 and T3 ($96,200 vs. $89,300, $p = 0.0134$). Conclusion: There was no difference in patients' socio-demographic data nor a mortality or routine discharge difference in the time periods examined from the beginning, middle, and end of the academic calendar. There is a small difference in length of stay and hospital cost, which is of questionable clinical significance. Given that the increased hospital charges may be attributable to operative or hospital ward factors, further investigation may be warranted.

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Is the Number of Transarterial Chemoembolization Treatments in Hepatocellular Carcinoma Patients Associated with Improved Survival?: A SEER Medicare Population Analysis F.T. Shaya,[1]* I.M. Breunig,[1] N. Hanna,[2] N. Pandya,[2] V. Chirikov,[1] B. Seal,[3] D. Mullins.[1] *1. University of Maryland School of Pharmacy, Baltimore, MD; 2. University of Maryland School of Medicine, Baltimore, MD; 3. Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ.*

Introduction: To examine treatment patterns and associated survival outcomes of transarterial chemoembolization (TACE) at all stages of HCC in SEER Medicare. Methods: Medicare enrollees, 65 and older, with a diagnosis of a primary HCC between 2000-07 who received treatment were followed through end of 2009 using the Surveillance, Epidemiology and End-Results Program (SEER) and linked Medicare databases, with claims from Medicare parts A and B. Using Cox proportional hazards models, we assessed the impact on mortality of each additional TACE, systemic chemotherapy, SIRT, external beam radiation therapy, ablation and surgical resection, controlling for cancer stage, general health status, underlying liver disease (alcohol related, Hepatitis B and C, moderate/severe liver dysfunction), and demographics. We assessed overall and HCC-related mortality for all, then for TACE-only treated patients, and stratified outcomes by stage. Results: Out of 3322 treated non-transplant

HCC patients, 1094 got TACE, 74% were Caucasian, 6% African American, 66% male, and 45% were at stage 1/2, 17% stage 3 and 14% stage 4. Most (56%) received 1, 23% 2, 11% 3 and 10% 4 or more TACEs. In the adjusted models, both overall and HCC mortality reduction were associated with treatment with up to 2 TACEs (HR=0.68, P=<0.001 and HR=0.73, P=<0.001, respectively). A third TACE, but not a fourth, provided a further decrease in overall mortality (0.46, <0.001) and HCC mortality (.45, <0.001). When stratified by stage, the second TACE had a significant marginal effect within Stage 3, and only the first TACE had benefit within Stage 4. No effects were found for TACE in early HCC. Conclusions: TACE provides a survival benefit for elderly HCC patients in clinical practice. However, the survival benefit may decrease beyond 3 TACE treatments and varies by stage. Additional TACE treatments may be confounded if 4+ TACE treatments are utilized mainly to treat biologically aggressive disease related to extensive tumor burden, advanced disease or recurrences. Treatment selection bias cannot be excluded and should be further explored.

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Long-term Survival following Pancreatoduodenectomy for Pancreatic Adenocarcinoma G.A. Falk,* D. Joyce, M. Gareth, S. Chalikonda, R. Walsh. *Cleveland Clinic Foundation, Cleveland, OH.*

Introduction: Pancreatoduodenectomy for adenocarcinoma is meant to be curative but that goal is rarely achieve. Determination of factors that may predict longterm outcomes could impact selection of patients for aggressive resection. The aim of this study was to review the long-term results of pancreatoduodenectomy and to determine the histopathology of those surviving in excess of 5 years. Methods: The departmental database was reviewed to identify all patients undergoing pancreatoduodenectomy during the period January 2000 to December 2005, such that the minimal potential follow-up was 5 years. For all patients within this cohort, the histopathology was reviewed to determine the tumor type present. Results: During the study period 195 patients underwent pancreatoduodenectomy and 96 patients survived at least 5 years. Data for the primary adenocarcinomas of the peri-ampullary region are summarized below. The 5-year actual survival of patients with pancreatic ductal adenocarcinoma (29%) was significantly less than that of other periampullary neoplasms ($p<0.05$) despite a similar stage profile at presentation. Of those with pancreatic ductal adenocarcinoma, the initial disease staging was: IA (n=4); IB (n=13); IIA (n=8); IIb (n=52); III (n=0) and IV (n=1). Of stages of those surviving 5 years was: IA (n=4 [100%]); IB (n=8 [63%]); IIA (n=2 [25%]); IIb (n=11 [21%]); and IV (n=0 [0%]). Conclusion: Whilst the prognosis of patients with pancreatic adenocarcinoma undergoing resection is not as good as that of other periampullary neoplasms, the actual survival rate of 26% at 5 years indicates that success can be achieved. Furthermore, whilst prognosis is significantly better for stage I disease, patients with stage II disease exhibit survival of greater than 20%.

5 year survival of patients undergoing pancreatodudenectomy

Histopathology	Number resected	Number 5-year survivors (%)
Ampullary	35	18 (51%)
CBD	8	4 (50%)
Duodenum	15	10 (67%)
Pancreas	78	20 (26%)

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Tumor Location in Pancreatic Cancer Does Not Affect Lymph Node Ratio Despite Significant Difference in Lympho-vascular Invasion V. Siripurapu,* E. Liu, A. Khithani, D.R. Jeyarajah. *Dallas Methodist, Dallas, TX.*

Introduction: Pancreatic cancer mortality is dependent on node positivity, margin resection and overall stage of tumor. We aim to assess whether equivalent tumor (T) sizes for the standard procedures of distal pancreatectomy (DP) or pancreaticoduodenectomy (PD) for pancreatic cancer have varying nodal positivity ratios related to tumor location Methods: A database of 89 patients with pancreatic cancer treated in 2009-2011 inclusive for operative type, patient co-morbidities, tumor pathology including a calculated nodal ratio (node positive/total nodes) was analyzed. Results: 50 patients with PD and 14 patients with DP were identified with pathologic T3 pancreatic adenocarcinomas. No pre-operative treatment was administered for either group. Mean age for these two groups was 67.4±3.81 yrs (PD) and 65.1±12.9 yrs (DP) (p=NS). The patient mean modified co-morbidity score for PD and DP was 2.86±0.68 and 2.57±1.76 respectively (p=NS). BMI averaged was 26.0±1.82 for PD versus 27.9±4.47 for DP (p=NS). Nodal positivity was 74% in PD versus 64% in DP group (P=0.22) Lymphovascular invasion was significantly higher in the PD group 58% versus 29% (p=0.02). Mean number of nodes examined was 22.0±3.62 for PD versus 18.0±6.28 for DP (p=NS). Mean Node positive ratio was 3.54±1.62 for PD versus 3.86±3.56 for DP (p=NS). There were no operative mortalities. Values shown in Table 1. Conclusion: With an equal T stage between the two operative groups, nodal positivity and nodal ratio was similar in the pancreaticoduodenectomy and distal pancreatectomy groups with an equal number of total nodes identified. This suggests that tumor location does not have a bearing on ease of nodal spread based on equivalent tumor size despite varying lympho-vascular invasion.

Table1. Patients Undergoing Pancreaticoduodenectomy and Distal Pancreatectomy

	Pancreaticoduodenectomy	Distal Pancreatectomy	p value
Number of Patients	50 (78)	14 (22)	
Mean Age (yrs)	67.4±3.81	65.1±12.9	[NS]
Gender			
Male	28 (56)	10 (71)	[NS] p=0.8438
Female	22 (44)	4 (29)	[NS] p=0.1562
Mean Co Morb Index	2.86±0.68	2.57±1.76	[NS]
Mean BMI	26±1.82	27.9±4.47	[NS]
Mean Nodes Examined	22±3.62	18±6.28	[NS]
Mean Nodes Positive	3.54±1.62	3.86±3.56	[NS]
Lymph-Vascular Invasion	29 (58)	4 (29)	[S] p=0.0274
Number node +	37 (74)	9 (64)	[NS] p=0.2296

Percentages in parentheses
[NS] no significant difference
[S] significant difference

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Gd-EOB-DTPA MRI Enhanced the Ability of the Preoperative Diagnosis of Hepatocellular Carcinoma S. Aoki,* T. Sugiura, H. Kanemoto, T. Mizuno, Y. Okamura, T. Yamamoto, K. Uesaka. *Shizuoka Cancer Center, Shizuoka, Japan.*

Objective The aim of current study is to investigate whether gadolinium-ethoxybenzyl-diethylenetriamine (Gd-EOB-DTPA) enhanced MRI (EOB-MRI) can improve the preoperative diagnostic ability of hepatocellular carcinomas (HCCs) compared to conventional modalities such as multidetector computed tomography (MDCT) and abdominal ultrasonography (Abd-US). Method Between March 2009 and August 2010, a total of 201 nodules were preoperatively examined by EOB-MRI, MDCT, and Abd-US. One hundred twenty-two nodules were resected and pathologically diagnosed as HCCs in 109 and non-HCCs in 13. Remaining 79 nodules were not resected, radiologically followed at least 1 year, and concluded as non-HCCs because of no morphological change. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of each imaging modality were calculated. Results The sensitivity, specificity, PPV, NPV and accuracy were 90.8%, 94.6%, 95.2%, 88.8%, and 92.5% in EOB-MRI, 74.3%, 100%, 100%, 76.7%, and 86.5% in MDCT, 71.6%, 97.8%, 97.5%, 74.4%, and 83.6% in Abd-US, respectively. The sensitivity and accuracy of EOB-MRI were significantly better than those of MDCT ($p<0.001$ and $p=0.023$) and Abd-US ($p<0.001$ and $p=0.007$). Among the 109 HCCs, 81 were detected by EOB-MRI and either MDCT or abd-US (conventional group), 18 were detected only by EOB-MRI (EOB-MRI group), and 10 were not detected by any preoperative modalities. Eighty-one HCCs in the conventional group comprised moderately differentiated HCCs (mod-HCCs) in 80 and poorly differentiated HCCs in one. Among 18 HCCs in the EOB-MRI group, 11 were well differentiated HCCs (well-HCCs) and 7 were mod-HCCs. The size of these 7 mod-HCCs in EOB-MRI group (median 5 mm) was significantly smaller compared to that of 80 mod-HCCs in the conventional group (median 23 mm) ($p=0.006$). Conclusion EOB-MRI is useful for detecting HCCs, particularly well-HCCs and small mod-HCCs.

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Clinical Magnitude of a Large Intervening Non-coding RNA, HOTAIR in Solid Carcinomas I. Msahisa,[1]* K. Mimori,[1] G. Sawada,[1] Y. Takahashi,[1] R. Kogo,[1] T. Akagi,[1] N. Nishida,[1] T. Iwaya,[1] T. Sudo,[1] F. Tanaka,[1] K. Shibata,[1] M. Mori.[2] *1. surgery, Kyushu university Beppu hospital, Beppu,Oita, Japan; 2. Department of Gastroenterological surgery of Osaka University, Yamadaoka 2-2, Suita city, Osaka prefecture, Japan.*

It has been gradually unveiled that non-coding RNA has many functions. In particular, some of large intervening non-coding(linc)RNA is focused on implicating cell cycle regulation, immune surveillance, and stem cell pluripotency. Recently, Gupta et al. disclosed that one of the linc RNAs, HOTAIR was an independent prognostic marker in patients with breast cancer. HOTAIR recruits the PRC2 complex to specific target genes genome-wide, leading to H3K27 trimethylation and epigenetic silencing of metastasis suppressor genes. In the current study, we have much focused on the clinical significance of HOTAIR, such as colorectal cancer(CRC) and hepatocellular carcinoma(HCC). We examined relevance of expression of HOTAIR and clinicopathological factors in 100 cases of CRC and 64 cases of HCC operated in our hospital from 2002 to 2006. Total RNA was obtained by ultracentrifugation through a cesium chloride cushion. For HOTAIR quantitative real-time polymerase chain reaction (qPCR), cDNA was synthesized from 10ng of total RNA using HOTAIR specific primers and analyzed the clinicipathologic significance. As for CRC cases, HOTAIR expression level is significantly higher in cancer tissues than the corresponding normal tissues (P=0.002). HOTAIR high expression is intimately correlated with liver metastasis (P=0.009) and the patients of HOTAIR high expression have a significantly poorer prognosis for overall survival (P<0.001). Among 64 cases of HCC, 13 cases showed positive expression for HOTAIR, however, the remaining 51 cases exhibited absent expression . We found HCC cases with HOTAIR expression indicated poorer prognosis than those without expression (p<0.05), and there was no significant association with any clinicopathologic factors. Therefore, we validated HOTAIR was an independent factor in HCC cases as other malignancies. In addition, we performed GSEA and found the abundant expression of the cluster of HOTAIR-induced PRC2(SUZ12, EZH2, and H3K27me3)were significantly observed in primary CRC(P<0.05). Solid cancer cases with the abundant expression of HOTAIR in primary tumors indicated poor prognosis than those without expression of HOTAIR.

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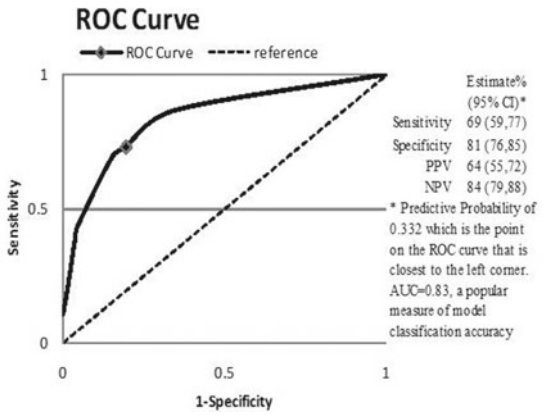
Predictors of Incidental Gallbladder Cancer in Patients Undergoing Cholecystectomy for Benign Gallbladder Disease V.P. Koshenkov,[1]* T. Koru-Sengul,[2] P.J. DiPasco,[1] M.S. Carter,[3] D. Franceschi,[2] S.E. Rodgers.[2] *1. University of Miami Miller School of Medicine, Miami, FL; 2. Sylvester Comprehensive Cancer Center, Miami, FL; 3. Atlantic Health, Morristown, NJ.*

Introduction: Over the past two decades, cholecystectomy for gallbladder disease has become more frequent due to adoption of laparoscopy. The discovery of incidental gallbladder cancer (IGC) remains a dilemma for general surgeons worldwide. Gallbladder spillage during the operation can disseminate the cancer and upstage the patient's disease. Methods: All patients who underwent laparoscopic or open cholecystectomy for benign gallbladder disease from 1/1996 to 8/2011 at two tertiary care facilities were reviewed. Laparoscopic approach was utilized in 87% of the cases. Unmatched controls were randomly selected for 67 patients with IGC from a group of patients in the study period in a 2:1 ratio. Variables such as age, sex, diagnosis, presence of gallstones, large gallstones, polyps, gallbladder wall thickening, dilated bile ducts (extrahepatic or intrahepatic), elevated liver function tests, and low albumin were compared between the two groups. Results: A total of 201 patients were included, with mean age of 68 for cases and 49 for controls; 70% of cases and 75% of controls were female. The two groups had statistically significant differences in age, presence of gallbladder wall thickening, dilated bile ducts, elevated LFTs and low albumin in unadjusted analysis. Multivariate analysis showed that higher risk of IGC was significantly associated with age ≥65 (OR=10.61, p<0.0001), dilated bile ducts (OR=4.76, p=0.0028), and presence of gallbladder wall thickening (OR=4.39, p=0.0003). This model yielded an excellent area under the curve of receiver operating characteristic (AUC=0.83). (See Figure) Conclusion: IGC is more likely to be found in patients presenting for cholecystectomy for benign gallbladder disease when age is ≥ 65, with dilated bile ducts and gallbladder wall thickening identified during preoperative work-up. Preoperative suspicion of gallbladder cancer should prompt the surgeon to be much more careful not to perforate the gallbladder during laparoscopic approach, to use a retrieval bag for the specimen, and to have a lower threshold for conversion if necessary.



P253

PLOD2 Induced under Hypoxia is a Novel Prognostic Factor for Hepatocellular Carcinoma after Curative Resection T. Noda,[1]* H. Yamamoto,[2] I. Takemasa,[2] D. Yamada,[2] M. Uemura,[2] H. Wada,[2] S. Kobayashi,[2] S. Marubashi,[2] H. Eguchi,[2] M. Tanemura,[2] K. Umeshita,[3] Y. Doki,[2] M. Mori,[2] H. Nagano.[2] *1. Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan; 2. The Department of Surgery, Osaka University, Suita, Japan; 3. The Department of Health Science, Osaka University, Suita, Japan.*

Background: Under hypoxic conditions in most cancers, tumor cells undergo genetic and adaptive changes that allow their survival and even proliferation. Previously, we reported that high expression of hypoxia-inducible factor (HIF)-1 was a significant predictive factor for recurrence in hepatocellular carcinoma (HCC) patients. Hypoxia also stimulates expression of procollagen-lysine, 2-oxoglutarate 5-dioxygenase (PLOD) genes via the HIF-1 pathway. Aims: The aim was to evaluate the relationship between hypoxia stress and expression of PLOD genes in HCC in vitro and to identify a new prognostic marker in HCC patients. Methods: The PLOD2 expression was assessed under hypoxia in hepatoma cell lines and characterized in 139 HCC samples following hepatic resection by microarray experiments, quantitative RT-PCR, and immunohistochemistry. Prognostic factors in HCC patients were assessed by univariate and multivariate analyses. Results: The PLOD2 expression was induced under the hypoxia in vitro. Disease-free survival in the high PLOD2 expression group of HCC patients was significantly shorter compared to the low-expression group (P=0.002). In a subset of HCCs, we found that the PLOD2 expression of microarray was correlated with data of quantitative RT-PCR and immunohistochemistry. Of clinicopathological factors, PLOD2 expression was significantly correlated with tumor size (P=0.022) and macroscopic intrahepatic metastasis (P=0.049). In univariate analysis, six prognostic factors (tumor multiplicity, macroscopic intrahepatic metastasis, histological grade, microscopic portal invasion, microscopic intrahepatic metastasis, and PLOD2 expression) were significant for disease-free survival. PLOD2 expression was identified as a significant, independent factor of poor prognosis (P=0.013). Conclusions: PLOD2 is a potential novel prognostic factor for HCC patients following surgery.

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Assessment of a New Predictive Score for Non-sentinel Node Positivity in Melanoma Patients K.P. Wevers,[1]* R. Murali,[2] E. Bastiaannet,[1] R.A. Scolyer,[2] A.J. Suurmeijer,[1] J.F. Thompson,[2] H.J. Hoekstra.[1] *1. University Medical Center Groningen, Groningen, Netherlands; 2. Melanoma Institute Australia, Sydney, NSW, Australia.*

Introduction. In melanoma, completion lymph node dissection (CLND) is performed in patients found to be sentinel node (SN) positive, with a positive non-sentinel node (NSN) found in roughly 1 out of 5 patients. Recently Murali et al proposed a new scoring system for stratification of risk for NSN positivity: the non-sentinel node risk score (N-SNORE), based on analysis of CLND

results in 309 SN-positive patients. The aim the present study was to identify factors predicting NSN positivity in a cohort of Dutch patients and to assess the validity of the proposed N-SNORE. Methods. All patients who underwent a CLND after a positive SN biopsy between 1995 and 2010 were analyzed (n=130). Characteristics of patient, primary melanoma, and SN biopsy were tested for association with NSN positivity. Missing values were reconstructed using multiple imputation to enable multivariable analysis. Results. CLND revealed positive NSNs in 30 patients (23%). Seventeen patients (57%) showed involvement of a single NSN, whereas 13 patients (43%) had more than one node affected (range 2 - 12). Associated with NSN positivity in univariate analysis were primary melanoma regression (p=0.01), histologic type other than nodular (p=0.03), and larger size of largest metastasis in a SN (p=0.008). Multivariable analysis revealed primary melanoma regression (p=0.03) and size of largest metastasis in a SN (p=0.04) to be independent predictors for NSN positivity. After an adjustment because of missing data on perinodal lymphatic invasion, the N-SNORE proved to be a significant stratification model for our dataset (p=0.003), with 5.9% NSN positivity in the very low risk category and 75% NSN positivity in the very high risk category (Table 1). However, the lack of perinodal lymphatic invasion data may have reduced the predictive value of the N-SNORE. Conclusion. Our study found primary melanoma regression and larger size of the metastasis in a SN to be independent predictors of a higher risk for NSN positivity. Fair stratification of risk for NSN positivity was achieved after a minor adjustment of the recently proposed N-SNORE.

Table 1: Predictive value of N-SNORE in the original and the present dataset

	N-SNORE - MIA * (Murali et al)				N-SNORE - UMCG ** (Wevers et al)			
Risk category	Score	Percentage of dataset (n=309)	Percentage NSN positive	p	Score	Percentage of dataset (n=130)	Percentage NSN positive	p
Very low	0	2.6	0	<0.001	0	7.9	5.9	0.003
Low	1 – 3	40.7	6.4		1 – 2	25.5	13.3	
Intermediate	4 – 5	42.0	16.3		3 – 4	39.4	21.1	
High	6 – 7	11.7	44.4		5 – 6	23.5	34.6	
Very high	?8	2.9	77.8		7 – 8	3.7	75.0	

* Melanoma Institute Australia
** Dutch data University Medical Centre Groningen: score adjusted by subtracting points for perinodal lymphatic invasion; max score 8 points

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BRAF Inhibition in Melanoma Results in a More Favorable Tumor Microenvironment A. Fiedler, A. Cogdill, L.M. Rosenberg, C.R. Ferrone, K.T. Flaherty, D.P. Lawrence, J.A. Wargo.* *Surgical Oncology, MGH, Boston, MA.*

Introduction: Melanoma is the 6th most common cancer in the U.S. with an incidence that is rising rapidly. Though early stage disease may be cured with surgery, late stage disease is often fatal. Better forms of treatment are needed. Targeted therapy against BRAF is an exciting new therapeutic approach for the treatment of melanoma. Fifty to 60% of treated patients achieve objective responses, with 90% realizing some degree of tumor regression. However, nearly all patients relapse within 6-8 months. There has been intense research with regard to identifying strategies to overcome resistance to targeted therapy. We recently published results supporting combination with immunotherapy, showing a significant increase in melanoma antigen expression after treatment with a BRAF inhibitor. These findings were corroborated in patients treated with a BRAF inhibitor (under review for publication). We next sought to analyze components of the tumor microenvironment in melanoma patients on BRAF-targeted therapy to further support the rationale for combination with immunotherapy. Methods: Tumor biopsies were performed pre-treatment and 10-14 days after initiation of BRAF-targeted therapy in patients with metastatic melanoma. Formalin-fixed tissue was analyzed to confirm that viable tumor was present via hematoxylin and eosin (H&E) staining, and RNA was isolated from tumors. Differential expression of immunomodulatory cytokines IL-8,IL-10, TGF-beta, TNF, and IDO in patient samples was assayed via RT-PCR. Results: Treatment with a selective BRAF inhibitor resulted in a more favorable tumor microenvironment with a decrease in immunosuppressive cytokines (IL-8, IL-10, IDO) and and increase in immunostimulatory cytokines (TGF-beta and TNF) in the majority of patients (see chart). Though there was significant variability between individuals, there was concordance within the same individual. Conclusion: These results suggest that BRAF inhibition in melanoma results in a more favorable tumor microenvironment. This data has important clinical implications, and provides further support to the rationale for combining BRAF-targeted therapy and immunotherapy for the treatment of melanoma.

Expression of Immunomodulatory Cytokines in Tumors After BRAF-targeted Therapy

	IL-8	IL-10	IDO	TGF-beta	TNF
Decreased	6/12	7/12	6/12	2/12	1/12
No change	3/12	1/12	2/12	3/12	3/12
Increased	3/12	4/12	4/12	7/12	8/12

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Mathematical Model to Predict Risk for Lymphoedema after Treatment of Cutaneous Melanoma L.L. Campanholi,[1] J.P. Duprat,[1]* J.T. Fregnani.[2] *1. Skin Cancer, Hospital do Cancer Sao Paulo, São Paulo, São Paulo, Brazil; 2. Hospital do Câncer de Barretos, Barretos, Sao paulo, Brazil.*

Introduction: Few studies have sought to predict risk factors for development of limb lymphoedema after inguinal or axillary lymph node dissection performed as treatment for cutaneous melanoma. The impact of different treatment types and their complications has not been clarified by existing studies. The aims of this study were to evaluate the risk factors for lymphoedema development in the limbs and to propose a mathematical model that can predict the risk of limb lymphoedema after lymphadenectomy. Methods: We studied 84 patients who had undergone radical lymphadenectomies for cutaneous melanoma from 1990 to 2008. The patients included underwent an evaluation that consisted of measurement of limb volume using perimetry, application of the manually acquired perimetric data to the truncated-cone formula, and data from medical records. Results: Using multivariate analysis, we obtained the following risk factors for the development of lymphoedema: reconstruction with graft (p= 0.013), Breslow depth >4mm (p= 0.029), ilioinguinal lymphadenectomy (p= 0.037) and wound infection (p= 0.036). We assigned points to each factor as dictated by the value of the regression coefficient, as follows: infection (1 point), ilioinguinal lymphadenectomy and Breslow >4 mm (2 points each) and reconstruction with graft (3 points). The mathematical model for predicting lymphoedema risk in the limb ipsilateral to the lymphadenectomy was based on risk groups, defined by score: low risk= 0 point (for which we calculated an 8.3% chance of developing lymphoedema), intermediate risk= 1-2 points (26.8%), high risk= 3 points (52.9%) and very high risk= 4 or more points (88.9%). Conclusions: This study identified a melanoma thickness >4 mm, graft reconstruction, ilioinguinal lymphadenectomy and infection as risk factors for lymphoedema. From these factors, we constructed a mathematical model that successfully predicted risk of post-lymphadenectomy lymphoedema. The combined presence of these risk factors increased the chance of developing lymphoedema.

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Outcomes in Patients with Mucosal Melanomas D. Keller,[1]* A.A. Thomay,[2] J. Gaughan,[1] H. Wu,[2] J.M. Farma.[2] *1. Surgery, Temple University Hospital, Philadelphia, PA; 2. Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Mucosal melanoma is a rare, aggressive variant of melanoma with increasing incidence. While predictors of outcome are well described for cutaneous melanoma, there are no unique indicators for the mucosal sub-types. The purpose of this study is to evaluate the different subtypes of mucosal melanoma and describe specific variables that may predict outcomes. Methods: 53 patients with mucosal melanoma were identified from a retrospective review of a prospectively maintained database at a tertiary care center. Complete records for 40 patients were available for review. Analysis of demographic and clinical data was performed. Cox regression was used to determine variables that impacted recurrence and survival. Results: In the 40 patients, mean age was 67 +/- 15 years, and 73% were female. Four patients initially presented with metastatic disease, and 11 with lymph node involvement. Major sites affected were nasal/ palate/ oral (38%), vulvar/ vaginal/ cervical (44%), and anorectal (14%). Median survival was 31 months and median recurrence-free survival was 120 months. Univariate analysis variables associated with survival included: nasal/ palate/ oral sub-group (HR 4.24, p=.0013), M stage (HR 5.36, p=.0066), XRT (HR 4.70, p=.0021), and chemotherapy (HR 4.71, p=.0011). The worst prognosis was seen in the nasal/palate/oral sub-group, with a median survival time of 8.2 months and median recurrence-free time of 4.5 months (Figure 1). Accordingly, this subtype also demonstrated high lymph node positivity and larger tumor size. Of patients with head and neck tumors, the mean size was 2.76 cm and 43% had positive lymph nodes. Conclusion:

Results demonstrate the nasal/ palate/ oral subtype has the worst prognosis compared to other mucosal melanoma locations. Studies are ongoing to evaluate other pathologic and genomic variables that may predict outcomes.

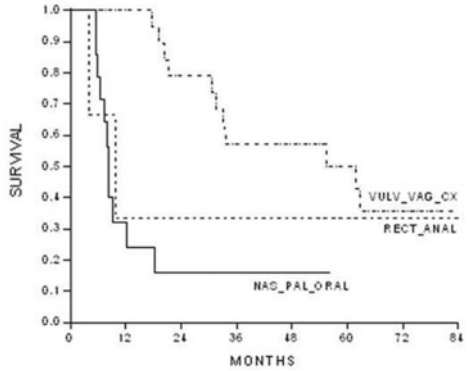

Figure 1: Survival Curve of Mucosal Melanoma by Subtype

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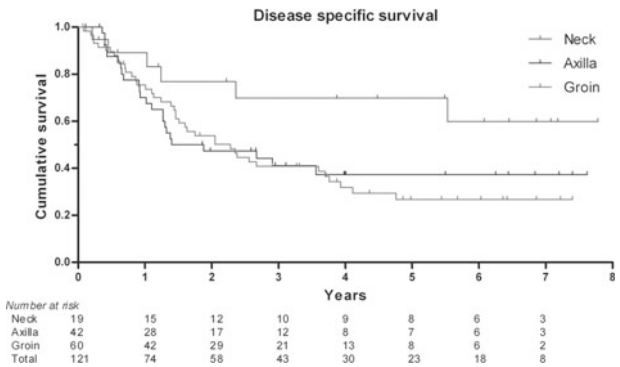
Outcome after Therapeutic Lymph Node Dissection in Melanoma: Different Prognosis for Different Sites of Macrometastasis K.P. Wevers,* H.P. Poos, E. Bastiaannet, R.J. Van Ginkel, J.T. Plukker, H.J. Hoekstra. *University Medical Center Groningen, Groningen, Netherlands.*

Introduction. The prognostic significance of primary tumor location, especially the worse prognosis for melanomas in the scalp and neck region, has frequently been studied. Recently Prens et al (Ann Surg Oncol, 2011) noticed a better prognosis after therapeutic lymph node dissection (TLND) if the nodal macrometastases were located in the neck. The aim of this study was to examine the prognostic value of the location of nodal macrometastasis in terms of recurrence and survival rates after TLND. Methods. We analyzed 121 FDG-PET staged melanoma patients with palpable and cytologically proven lymph node metastases operated on between 2003 and 2010. Multivariable analysis was performed to compare three different regional locations (groin, axilla, and neck) of nodal metastasis regarding disease free survival (DFS) and disease specific survival (DSS). Results. A total of 121 patients, 53 females (44%) and 68 males (56%) with median age of 58 (range 29-87) years, underwent a TLND; 60 groin (50%), 42 axillary (34%), and 19 neck (16%) dissections. The median follow-up for the entire group was 22 (range 1-93) months with an estimated 5-year DFS of 27% (95% CI: 18-36%), and an estimated 5-year DSS of 37% (95% CI: 27-46%). During the follow-up, 83 patients (69%) developed recurrent disease. Distant recurrence was the first sign of progressive disease in respectively 74%, 75%, and 44% of groin, axilla, and neck group (p=0.10). Multivariable analysis showed lower proportion involved / total nodes (p=0.003) and absence of extranodal growth pattern (p=0.01) to be independent predictors of longer DFS. For DSS, neck site of nodal metastasis (p=0.03), female gender (p=0.03), and lower proportion involved / total nodes (p=0.001) revealed to be independent predictors of longer survival. The estimated 5-year survival for DSS was for groin, axilla, and neck respectively 27%, 37%, and 70%. Conclusion. This study shows a significant longer disease specific survival after TLND for nodal macrometastases located in the neck, compared to the axillary and groin site.



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Does Treatment of the Primary Bias the Approach to Regional Lymph Nodes in Melanoma? J. Hiles,[1]* J. Ozao-Choy,[2] J. Howard,[3] H. Kargozaran,[4] M.B. Faries,[5] D.L. Morton.[6] *1. Surgical Oncology, John Wayne Cancer Institute, Los Angeles, CA; 2. John Wayne Cancer Institute, Los Angeles, CA; 3. John Wayne Cancer Institute, Los Angeles, CA; 4. John Wayne Cancer Institute, Los Angeles, CA; 5. John Wayne Cancer Institute, Los Angeles, CA; 6. John Wayne Cancer Institute, Los Angeles, CA.*

Background: Although nodal management based on sentinel lymphadenectomy improves the overall survival of patients with regional metastases from intermediate-thickness melanoma, many patients do not undergo nodal sampling. Why? We hypothesized that the technique used to remove the primary lesion influences the likelihood of histopathologic nodal assessment. Methods: Patients with histologically confirmed, clinically localized cutaneous melanoma were identified from the Surveillance, Epidemiology, and End Results database (2004-2007). Patients were excluded if lesions were T1a or <0.5 mm thick, or if treatment of the primary was uncertain or did not include excision. Regional node assessment was defined as any technique that yielded tissue for histopathologic analysis. Data included the patient's age and geographic location; the primary tumor's thickness, Clark level, ulceration, and anatomic site; and the treatment of the primary lesion. Student t-test and Chi squared test were used. Multivariate logistic regression model was used to assess the role of treatment of the primary on lymph node staging. Results: Of 19,708 patients who met study criteria, 13219 (67.1%) underwent regional node assessment. Treatment of the primary significantly affected the likelihood of regional node assessment ($p<0.0001$). Interestingly, only 125 of 294 (43%) patients undergoing Mohs micrographic surgery (MMS), and only 541 of 2051 (26%) undergoing biopsy alone had regional node assessment. By contrast, 139 of 175 (79%) of amputation patients, 8172 of 10365 (79%) wide local excision patients, and 4138 of 6512 (64%) biopsy+excision patients underwent regional nodal assessment. Multivariate analysis revealed that age, anatomic location, thickness, Clark level, ulceration, treatment of the primary, and geographical location all predicted inadequate regional node assessment ($p\leq0.001$). Conclusions: Patients whose cutaneous melanoma is managed by MMS or biopsy alone have a high (> 55%) risk of inadequate regional node assessment. Failure to remove a primary melanoma by wide local excision increases the chance that regional node status will not be considered.

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Detection of Cutaneous Melanoma: How Can We Find It Earlier? T.J. Hieken,[1]* V. Krishnamurthy,[3] J.E. Foster.[2] *1. Surgery, Mayo Clinic, Rochester, MN; 2. NorthShore University HeathSystem Skokie Hospital, Skokie, IL; 3. Rush University Medical Center, Chicago, IL.*

INTRODUCTION: Both the incidence of and mortality from melanoma (MM) is increasing. Survival is directly related to stage at diagnosis. MM is unique in its potential for early diagnosis by visual inspection of the skin. Older data suggest self-detected MMs are thicker than those found by physicians, but there is little current data on MM detection and its association with patient (PT) and tumor features. We undertook this study in an effort to identify strategies for improvement. METHODS: We reviewed questionnaire data obtained prospectively at the time of surgical oncology consultation for 488 newly diagnosed melanomas (MM) in 435 PTs and entered with demographic and tumor data into our Melanoma Registry. Data were analyzed with SAS statistical software. RESULTS: PTs detected most MMs (51%), followed by non-dermatology physicians (34%) and dermatologists (15%). Females more often detected their MMs (57%) than males (45%), p=0.02. Mean PT age was younger for PT vs MD-detected MMs (62 vs 71 yrs) and 70% of MMs in PTs ≤50 yrs were PT-detected, $p<0.001$. More extremity/head/neck than truncal ($p<0.001$) and more anterior than posterior MMs (p=0.03) were PT-detected. After a non-MM skin cancer PTs were more likely to be diagnosed by dermatologists (32%, $p<0.001$) who diagnosed 50% of insitu MMs. PT detection was associated with increasing tumor level and thickness, ulcerated and amelanotic MMs, all $p<0.001$, but not with MM diameter. Mean (median) tumor thickness was 1.66 (0.75) vs 0.72 (0.35) mm for PT vs MD-detected MMs with 66% of MMs >2mm thick PT-detected, $p<0.001$. The chief finding reported with PT-detected MMs was change in size (32%), color (31%) and bleeding (10%). In multivariate analysis, young age, no prior skin cancer, non-truncal site and >MM thickness were predictive of PT detection. CONCLUSIONS: Despite public health campaigns and increased awareness of melanoma, PTs still find the majority of MMs. PT-detected MMs remain thicker than MD-detected MMs.

Follow-up skin examination after non-MM skin cancer diagnoses thinner MMs. Efforts to increase awareness of melanoma among both PTs and physicians, focusing on PTs <age 50 and males, are needed to make strides in decreasing the lethality of MM.

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Lymphatic Mapping and Sentinel Lymph Node Biopsy for Melanoma of the External Ear T. Kidner,* H. Kargozaran, J. Yoon, M. Faries, D. Morton. *John Wayne Cancer Institute, Santa Monica, CA.*

Background: Melanoma of the external ear represents 1% to 4% of cutaneous melanomas and 15% of head and neck melanomas. Data regarding its management and sentinel lymph node (SN) drainage are limited. Patients and Methods: We queried our prospectively maintained melanoma database to identify patients treated for external ear melanoma between 1985 and 2011. Patient demographics, tumor characteristics, patterns of nodal drainage, incidence of SN metastasis, local and distant recurrence, and overall survival were examined. Results: One hundred thirty-four patients (87% male) were treated for melanoma of the external ear. Their mean age was 57 years (range 17-89). Seventy-one patients (53%) had melanoma on the left ear. Mean tumor thickness was 1.4 mm (range 0.1 – 6.0), and 19 tumors (14%) were ulcerated. SN biopsy was performed on 104 patients (77%). Drainage patterns were similar for all parts of the ear. The mean number of nodal drainage locations was 2 ± 0.7 (range 1 to 5). The mean number of SNs removed was 3 ± 2.2 (range 1 – 12). Twelve patients (12%) had SN metastases. Seven of these patients underwent completion lymphadenectomy with no additional positive nodes recovered. Of the 134 patients, 13 (10%) recurred locally and were treated with additional margins in all but one case for which a complete auriculectomy was performed. Twelve patients (9%) developed regional lymph node recurrence, and 17 (13%) developed distant metastasis. Mean time to first recurrence was 25.0 months (range 1.9 – 104.3). Univariate analysis of 5-year overall survival identified Breslow thickness and ulceration as negative prognostic factors, whereas superficial spreading histology had a positive influence on survival (Table 1). Ulceration remained significant on multivariate analysis (p=0.0133). Five-year overall survival was 68% for the SN-positive group and 81% for the SN-negative group (p=0.3681). Conclusion: To our knowledge, this is the largest single-institution analysis of external ear melanoma. This tumor appears to be heavily male predominant with a slight preference for the left ear. We recommend wide local resection with appropriate margins and SN biopsy.

Table 1: Univariate Analysis of 5-year Overall Survival (n=134)

	p-value	HR	95% CI
Breslow Thickness	0.0049	1.509	1.133 - 2.009
Ulceration	0.0133	3.595	1.305 - 9.899
Superficial Spreading	0.0434	0.403	0.167 - 0.973
Clark Level	0.0511	1.677	0.998 - 2.819
SN Positivity	0.3681	1.768	0.511 - 6.115
Posterior Helix	0.5597	0.766	0.313 - 1.875
Superior Helix	0.1002	0.387	0.125 - 1.200
Male Sex	0.8103	1.160	0.346 - 3.889

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Early Mobilization after Ilio-inguinal Lymph Node Dissection for Melanoma Does Not Increase the Wound Complication Rate K.P. Wevers,* H.P. Poos, H.J. Hoekstra. *University Medical Center Groningen, Groningen, Netherlands.*

Introduction. Ilio-inguinal lymph node dissection for stage III melanoma is accompanied by a substantial amount of wound complications. Our treatment protocols changed in time in terms of postoperative bed rest prescriptions, being in chronological order Group A: 10 days with a Bohler Braun splint, Group B: 10 days without splint, and Group C: 5 days without splint. The aim of this study was to evaluate the effect of bed rest prescriptions on wound complications. Patients and methods. For this study, we included all 193 patients who underwent an ilio-inguinal dissection for stage III melanoma in the period 1989-2011: 64 patients in Group A, 89 patients in Group B, and 40 patients in Group C. Both univariate and multivariable analysis were performed to identify factors that were associated with occurrence of wound complications defined as wound infection, wound necrosis, and seroma. Results. We analyzed 193 patients, consisting of 96 females (49.7%) and 97 males (50.3%) with a median age of 56 (range 5-91) years. Ninety-five patients (49.2%) suffered one or more wound complications: 47 wound infection (24.3%), 29 wound necrosis (15.0%), and 39 seroma (20.2%). A wound complication occurred in 26 out of 64 (40.6%), 51 out of 89 (57.3%), and 18 out of 40 patients (45.0%) for Group A, B, and C respectively. Univariate analysis showed age >55 (p=0.001) and presence of comorbidity (p=0.01) to be associated with higher incidence of wound complications. Multivariable analysis revealed age >55 (OR=2.42; 95%CI=1.26-4.61, p=0.008) and bed rest protocol used in group B (ref=Group A: OR=2.66; 95%CI=1.30-5.46, p=0.008) to be independently associated with occurrence of wound complications. The 5 day bed rest protocol used in group C did not significantly increase the incidence of wound complications (ref=Group A: OR=1.24; 95%CI=0.53-2.93, p=0.62). Conclusion. Changing 'bed rest protocols' to 5 days without Bohler Braun splint usage, did not significantly increase the incidence of complications after ilio-inguinal lymph node dissection for melanoma.

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Transferring Innovative Freehand SPECT to the Operating Room: First Experiences with Sentinel Lymphonodectomy in Malignant Melanoma J. Saeckl, A. Rieger,* T. Wendler. *Surgery, Klinikum rechts der Isar, Munich, Germany.*

Introduction: Sentinel Lymph Node Biopsy (SLNB) in melanoma using one dimensional gamma probes is the standard procedure worldwide. Most groups report to successfully detect the SLNs during the surgical procedure in almost 100% of the patients. In clinical practice, however, several issues remain which are usually not addressed: the difficulty of intraoperative detection of deeply located nodes, SLN detection in obese patients or in the groin and the impossibility to to make a scan of the entire wound after SLN resection to avoid false negative testing for eventually remaining SLNs. Materials and methods: The concept behind freehand SPECT is to combine a gamma probe as used for conventional radio-guided surgery with a tracking system as used in neurosurgical navigation. From this combination and a proper algorithm framework the 3D-reconstruction of radioactivity distributions and displaying these intraoperatively is possible. Twenty consecutive patients with histologically diagnosed malignant melanoma and a tumour thickness of more than 1mm, who underwent SLN mapping, were enrolled in this study. The location of the primary melanoma was on the lower arm, on an upper arm, a shoulder, on the back, on the side of the torso, on the side of the abdomen and on the lower leg. After surgery, the findings of the biplanar scintigraphy, the freehand SPECT images and the histological examination results were compared. Conclusion: In summary, the feasibility of freehand SPECT could be shown and provides an image-guided SLNB and a truly minimally invasive and optimized surgical procedure. The freehand SPECT system provides several advantages to the actual standard using planar SPECT and gamma probe. A further randomized multicentre study involving a high number of patients is currently planned and will be published later.

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Impact of PET/CT at the Time of Clinically Detected Regionally Recurrent Cutaneous Melanoma J. Samples,* M.O. Meyers, A.M. Deal, J.J. Baker, J.S. Frank, D.W. Ollila. *Universtiy of North Carolina, Chapel Hill, NC.*

Introduction: PET/CT is a commonly performed staging study for patients with cutaneous melanoma. We have previously shown that PET/CT is unlikely to detect unsuspected disease at the time of diagnosis of sentinel lymph node (SLN) positive melanoma. We sought to evaluate the impact of PET/CT at the time of clinically detected regional recurrence. Methods: A prospective, IRB-approved, single-institution database was queried to identify patients treated at our institution from 2003-2011 who developed a clinically detected regional recurrence (self-detected by a patient or by a physician on routine exam) and were staged with PET/CT. Fisher's exact test and log-rank test assessed the association between clinical and demographic variables and the likelihood of a positive PET/CT. Results: 76 patients met criteria for inclusion. Median age: 58 years(range 25-90). Initial histologic data: median Breslow depth 2.8mm(range 0.25-11.5). 39 ulcerated and 56 with mitotic rate >1/mm2. 39 SLN negative, 24 SLN positive, 13 clinically node positive. 16(21%) PET positive for distant metastatic disease at the time of clinically diagnosed regional recurrence. There were no associations between any demographic or pathologic factor and the likelihood of a positive PET/CT. Time to recurrence(TTR) was associated with a positive PET/CT, with a shorter TTR more likely to have a positive study (median TTR 4.3 mo with positive PET/CT(95% CI: 0.22-0.89) vs. 10.8

mos for negative PET/CT(95% CI: 0.71-1.27)(p=0.05). Median post-recurrence survival was 2.5 years(95% CI: 1.74-4.00) for the entire group and was significantly shorter for those with a positive PET(1.1 yrs (95% CI:0.67-.93) vs. 2.7 yrs (95% CI:2.34-5.29) p=0.001). Conclusion: Patients with clinically detected regionally recurrent cutaneous melanoma often have additional disease detected with PET/CT, particularly in those with a short disease-free interval. This has the potential to dramatically impact treatment in the era of effective systemic therapy. Radiographic staging should be strongly considered in these patients, even in those who may have been staged at the time of diagnosis and have early regional recurrences.

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Intralesional Injection of Melanoma with Rose Bengal Induces Regression of Untreated Synchronous Melanoma in a Murine Model P. Toomey,* L. Martin, A. Mckay, A. Sarnaik, S. Pilon-Thomas. *H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.*

Introduction: Rose Bengal is a xanthene dye that has been used for liver function studies since 1923 and is currently used topically in ophthalmology. Intralesional Rose Bengal (PV-10) has been shown in clinical trials to induce regression of treated melanoma lesions and uninjected bystander lesions. This study was undertaken to confirm the apparent systemic effect of PV-10 to induce regression of bystander melanoma masses in a murine model. Methods: Two studies were undertaken with C57BL/6 mice. In the initial study, mice received subcutaneous (s.c) B16 melanoma cells to establish a solitary flank tumor and intravenous B16 to establish multiple lung metastases. On day 7, the s.c. tumor was treated with intralesional PV-10; intralesional phosphate buffered saline (PBS) was used in control mice. The mice were sacrificed on day 21 to enumerate the lung masses. In a second study, mice were implanted in bilateral flanks with B16 cells, and the resulting right tumor injected with PV-10 or PBS on day 7. Tumor sizes were measured regularly for both the right (treated) and left (untreated/bystander) s.c. tumors. Results: C57BL/6 mice treated with PV-10 had significantly fewer induced lung metastases than mice treated with PBS ($p<0.05$). Three out of five mice treated with PV-10 had three or less lung metastases; all control mice treated with PBS had over 250 lung metastases. C57BL/6 mice with bilateral tumors had a significant regression of tumors injected with PV-10 ($p<0.05$) and there was a trend in reduction in the untreated flank melanoma compared to mice treated with PBS. Conclusion: Patients with metastatic melanoma have a dismal prognosis. PV-10 has shown promise in treating metastatic melanoma in clinical trials, where it has led to objective responses of both injected and uninjected tumors. Regression of untreated melanoma masses by intralesional injection of concomitant masses suggests a systemic effect. These studies confirm that PV-10 therapy results in both a direct effect on treated melanoma lesions as well as a systemic response that leads to regression of synchronous lung metastases or synchronous subcutaneous melanoma.

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Unique Considerations for Performing Upper Extremity (UE) Isolated Limb Infusions (ILI) G. Beasley,[1]* J. Wong,[2] K. Sharma,[1] R. Turley,[1] L. Michael,[1] J.S. Zager,[2] D.S. Tyler.[2] *1. Duke University, Durham, NC; 2. Moffitt Cancer Center, Tampa, FL.*

Background: Delivery of regional chemotherapy to an UE using ILI with melphalan is different than ILI of the lower extremity (LE) although both are often combined for analysis. Methods: Prospective databases from 2 institutions identified patients undergoing ILI of the UE (n=48) and LE (n=134). The Response Evaluation Criteria in Solid Tumors and Weiberdink toxicity scale were used where appropriate. Results: Indications for UE ILI were: 77% (37/48) melanoma, 10.5% (5/48) sarcoma, 6.25% (3/48) Merkel cell, and 6.25% (3/48) squamous cell. As expected, UE ILI had lower limb volumes (2.5 L vs. 9.2 L, $p<0.001$) and subsequently lower melphalan doses (20.5 mg vs. 52 mg, $p<0.001$). Interestingly, on perfusate blood gas analysis, base excess at 30 minutes (-13.2 vs. -9.4, $p<0.001$) and pH at 30 minutes (7.05 vs. 7.13, $p<0.001$) were lower for UE vs LE procedures without differences in ischemic time (70.4 vs 73.9 minutes) or peak temperature (38.6°C for both). The CR rate for melanoma UE procedures was 27% (95% CI: 15-43%) compared to a CR of 31% (95% CI: 23-39%) for LE ILI. Regional toxicity ≥ Grade 3 after UE ILI was 6% compared to 34% ($p=0.005$) for LE ILIs while peak creatine kinase was also lower in UE ILI (900 U/L vs 1811, $P=0.04$). Conclusion: ILI for UE disease is associated with similar CR rates but lower toxicity than LE ILI and different physiologic sequelae despite comparable methods. The UE appears resistant to toxic effects of ILI as currently performed which suggests a potential for further optimization of drug dosing for UE ILI.

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Diversity of Stage III Melanoma in the Era of Sentinel Lymph Node Biopsy M.E. Egger,[1]* G.G. Callender,[1] K.M. McMasters,[1] M.I. Ross,[2] R.C. Martin,[1] M.J. Edwards,[3] M.M. Urist,[4] R.D. Noyes,[5] J.J. Sussman,[3] D.S. Reintgen,[6] A.J. Stromberg,[7] C.R. Scoggins.[1] *1. University of Louisville, Louisville, KY; 2. University of Texas M.D. Anderson Cancer Center, Houston, TX; 3. University of Cincinnati, Cincinnati, OH; 4. University of Alabama at Birmingham, Birmingham, AL; 5. LDS Hospital, Salt Lake City, UT; 6. Lakeland Regional Cancer Center, Lakeland, FL; 7. University of Kentucky, Lexington, KY.*

Introduction: Sentinel lymph node (SLN) biopsy for melanoma often detects minimal nodal tumor burden. Although all node-positive patients are considered stage III, there is controversy regarding the necessity of adjuvant therapy for all patients with tumor-positive SLN. Methods: A post-hoc analysis was performed of a prospective multi-institutional study of patients with melanoma ≥ 1.0 mm Breslow thickness. All patients underwent SLN biopsy; completion lymphadenectomy was performed for patients with SLN metastasis. Kaplan-Meier analysis of disease-free survival (DFS) and overall survival (OS) and univariate and multivariate Cox regression analyses were performed. Classification and regression tree (CART) analysis was also performed. Results: A total of 509 patients with tumor-positive SLN were evaluated with a median age of 48 years, median Breslow thickness (BT) of 2.3 mm, and median follow-up of 58 months. Factors predictive of overall survival (OS) on multivariate analysis are shown (Table). Tumor-positive non-SLN (nodal metastasis found on completion lymphadenectomy) was the strongest nodal factor predictive of OS. As the number of total tumor-positive nodes (sentinel and non-sentinel) and total tumor-positive SLN increased, DFS and OS worsened on Kaplan-Meier analysis. On CART analysis using Cox proportional hazards models, the 5-year OS rates ranged from 84.9% (women with BT < 2.1mm, Age < 59, no ulceration, and tumor-negative non-SLN) to 14.3% (men with BT ≥ 2.1mm, Age ≥ 59, ulceration present, and tumor-positive non-SLN). Six distinct subgroups were identified with 5-yr OS in excess of 70%. Conclusions: Stage III melanoma in the era of SLN biopsy is associated with a very wide range of prognosis. CART analysis of prognostic factors allows discrimination of low risk subgroups for which adjuvant therapy may not be warranted.

Factors associated with overall survival in Stage III melanoma

Variable	Multivariate Risk Ratio (95% CI)	Multivariate P-value
Breslow thickness≥ 2.1 mm	1.73 (1.24, 2.45)	0.0011
Age ≥ 59	1.78 (1.32, 2.37)	0.0002
Male gender	1.53 (1.13, 2.10)	0.0054
Ulceration	1.78 (1.33, 2.39)	0.0001
Tumor-positive non-SLN	1.51 (1.01, 2.20)	0.0467

CI, confidence interval; SLN, sentinel lymph node

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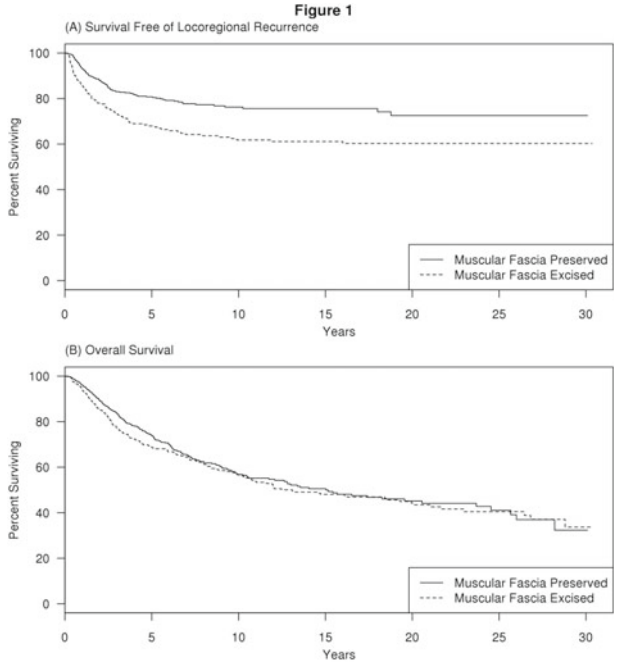
Preservation of the Deep Muscular Fascia Improves Locoregional Control in Melanoma T.E. Grotz,[1]* J.M. Glorioso,[1] B.A. Pockaj,[2] W.S. Harmsen,[1] J.W. Jakub.[1] *1. General Surgery, Mayo Clinic, Rochester, MN; 2. Mayo Clinic, Scottsdale, AZ.*

Background: Locoregional recurrence (LRR) occurs in approximately 10-20% of patients with melanoma and is associated with a significantly worse prognosis. Standards are well established for peripheral margins: however, there is insufficient evidence regarding depth of resection. Our aim was to analyze the effect of resection or preservation of the deep muscular fascia on the LRR of primary cutaneous melanoma. Methods: Retrospective review of 964 patients with primary cutaneous melanoma ≥ 1 mm thick of the trunk and extremities over a 28-year period that underwent wide local excision at a tertiary academic center. Multivariate analysis and hazard ratios were utilized to determine the effect of resection versus preservation of the muscular fascia on LRR. Results: 278 (29%) patients underwent resection of the muscular fascia. Of these patients, 18 (6%) developed local, 33 (12%) developed in-transit and 68 (24%) developed nodal recurrence at 5 years. The 1, 5 and 10 year survival free of LRR were 86%, 68% and 62% for patients whose fascia was excised, respectively.

686 (71%) patients underwent excision of their primary melanoma with preservation of the deep muscular fascia. Of these patients, 40 (6%) developed local, 30 (4%) developed in-transit and 84 (12%) developed nodal recurrence at 5 years. The survival free of LRR was greater ($p < 0.001$) for patients whose fascia was preserved, 93%, 81% and 76% at 1, 3 and 5 years, respectively (Figure IA). In multivariable analysis, excision of the deep muscular fascia was an independent predictor of both in-transit (HR 2.1 95% CI 1.3-3.5 $p = 0.004$) and nodal recurrence (HR 1.6 95% CI 1.1-2.3 $p = 0.009$). However, excision or preservation of the fascia did not influence overall survival ($p=0.9$) (Figure IB). Conclusion: Excision of the deep muscular fascia is associated with an increased risk of in-transit and nodal recurrence but not local recurrence or worse overall survival. Based on no demonstrated advantage for resection of the deep muscular fascia, but decreased disease-free survival, we recommend routine preservation of the fascia during resection of primary cutaneous melanoma.

Figure 1



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The Additional Value of Lymphatic Mapping with Routine SPECT/CT in Unselected Patients with Clinically Localized Melanoma H.J. Veenstra,[1]* L. Vermeeren,[2] R.A. Valdés Olmos,[1] O.E. Nieweg.[1] *1. Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 2. Academic Medical Centre, Amsterdam, Netherlands.*

Objectives: To investigate whether SPECT/CT is of additional value compared to conventional lymphoscintigraphy in routine lymphatic mapping in patients with cutaneous melanoma. Methods: Thirty-five unselected patients with a primary melanoma who were scheduled for wide local excision and sentinel node biopsy underwent conventional lymphoscintigraphy and subsequently SPECT/CT. We determined whether SPECT/CT showed additional sentinel nodes, provided better information on the location of the sentinel nodes and whether this additional anatomic information led to a change in the planned surgical approach. Results: SPECT/CT depicted the same 69 sentinel nodes as conventional lymphoscintigraphy in all 35 patients plus eight additional sentinel nodes in seven patients (20%). In two of these patients (5.7%) an additional nodal basin had to be explored to find the extra sentinel nodes. SPECT/CT provided additional anatomic information that was helpful to the surgeon in eleven patients (31%) and led to an adjustment of the surgical approach in ten patients (29%). Conclusion: SPECT/CT provided relevant additional information in 16 of the 35 patients (46%). Routine use of SPECT/CT in addition to conventional lymphoscintigraphy is recommended in melanoma patients undergoing lymphatic mapping. No Disclosures No Financial Interest

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Electrochemotherapy for Treatment of Locally Advanced Superficial Cancer: Results from a Single Institution E. Pennacchioli,* C. Margarino, F. Verrecchia, G. Tosti, G. Spadola, F. Baldini, M. Mosconi, P. Ferrucci, F. Cataldo, A. Testori. *Melanoma and Sarcoma Surgery, European Institute of Oncology, Milan, Italy.*

Introduction: ECT (elettrochemotherapy) has been widely used for the treatment of local superficial spreading of primary cutaneous cancer, metastatic cutaneous cancer and secondary cutaneous tumors. Methods: Between 2006 and 2011, 179 ECT treatments in 108 evaluable patients treated at IEO, Milan. Of patients treated for primary disease (62 pts), 40% (25/62) are squamous cell carcinoma, 37% (23/62) are basal cell carcinoma and 8% (5/62) are melanoma. In the group of patients treated for metastatic disease 76% (89/117) are melanoma. The treatment was performed using intravenous Bleomycin in 159 cases (89%), local Bleomycin in 20 cases (11%). 65% of patients had at least 2 treatments, 13% more than 3 treatments. Post-operative monitoring of response is recorded as clinical evaluation and direct digital imaging in all patient at day 30, 90, 180, 360. Results: One month after treatment were recorded as follows: CR 12% of cases, PR in 84% of cases; NR in 4% of cases; at three months CR 14%; PR 47% PRO 26% and 5% DOD; one year after treatment 18% CR; 25% PR 40% PRO and 10% DOD. The mean length of response in melanoma was for 3 months (mean 2-8 mos). Concerning the histotype, CR was obtained in 57% cases of Kaposi sarcoma and in 50% of BCC and 9% of melanoma. PR was obtained in melanoma in 89% of cases at one month, 35% at 6 months and 25% at one year. The treatment was never used to obtain surgical operability. The impact of the procedure on survival was not evaluated, as ECT is a local treatment. Local toxicity consist in mild pain, self-retaining serum effusion for at least couple of weeks and rare ulceration of treated nodules. A possible systemic effect of this treatment is being studied in our Institution, as an immunological effect has been considered. Conclusion: ECT is a safe procedure. In relation to the histotype it should be considered a palliative local treatment (melanoma, breast cancer) or a definitive curative treatment (Kaposi sarcoma and BCC). The length of response should be used in order to associate a systemic treatment, possibly an immunotherapy.

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Evaluating a Nomogram for Predicting Sentinel Lymph Node Status in Cutaneous Melanoma M.G. Mount,* R.K. Orr, C.L. Nguyen, R.B. Hird. *Surgery, Spartanburg Regional Healthcare System, Spartanburg, SC.*

Introduction: The Memorial Sloan-Kettering nomogram was created to predict the likelihood of sentinel lymph node positivity, a vital prognostic factor in cutaneous melanoma. The nomogram variables are patient age, Breslow depth, Clark level, location and presence of ulceration. Although two published series show that the nomogram is a good risk predictor, its value in clinical practice is unclear. Methods: Data were collected from consecutive cases of a surgical oncologist experienced in the treatment of melanoma from 2001 to 2010. In general, sentinel node biopsy was performed in all healthy patients with thickness >=1 mm, and offered to those >=0.75mm. All patients underwent excision of the primary lesion and sentinel node biopsy with radionuclide injection and lymphoscintigraphy. Sentinel nodes were serially sectioned and examined with H&E and S-100 stains. Nomogram probability of sentinel node positivity was calculated and compared to the final pathology. Receiver Operating Characteristics (ROC) curves were analyzed to determine the discrimination of the nomogram. Results: 108 patients met inclusion criteria. Average age was 55. Mean depth of invasion was 2.05 mm. Median Clark level was 4. Ulceration was present in 26.8% of lesions. Mean predicted nomogram probability of nodal metastasis was 13%, and sentinel node was positive in 16.6% of lesions. Discrimination was good with the area under the ROC curve 0.74 (95% CI 0.61-0.88), but individual risk grouping was inaccurate (Hosmer-Lemeshow "goodness of fit statistic" NS). {See table} 2/28 patients with a predicted node probability of metastasis of less than 5% were found to have positive sentinel lymph nodes. Conclusion: The nomogram is a useful tool for determining patients at high risk of sentinel lymph node metastasis. Although helpful for patient discussions, overreliance on the model may understage patients with low risk melanoma. In order to appropriately offer sentinel lymph node biopsy, further clarification on the risk of thin lesions is needed.

Nomogram	n	n SLN+	Expected %	Actual %
<5%	28	2	3.53	7.14
6-10%	33	1	7.84	3.03
11-20%	28	8	15.85	28.57
>20%	19	7	31.84	36.84

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0.75mm Breslow Index as Standard Cut-off in Sentinel Lymph Node Biopsy for Melanoma V. Moutinho,[1]* E. Akaishi,[1] E. Utiyama,[1] G. Mendes,[2] F. Teixeira,[2] F. Ferreira,[2] A. Perina,[2] S. Rasslan.[3] *1. University of Sao Paulo - School of Medicine, Sao Paulo, Sao Paulo, Brazil; 2. ICESP Cancer Institute - FMUSP, Sao Paulo, Sao Paulo, Brazil; 3. LIM 62 - FMUSP, Sao Paulo, Sao Paulo, Brazil.*

Introduction: Breslow index is the most important risk factor for melanoma progression. Breslow index cutoff to perform sentinel node biopsy is not consensual among institutions worldwide. Our study aims to discuss if 0.75mm is an adequate cut-off for sentinel node biopsy for melanoma. Methods: Retrospective charts from initial 115 patient files from May/2008 to June/2011 were analyzed. Sentinel lymph node biopsy was routinely carried out in patients with Breslow >0.75mm and in high risk patients with Breslow < or =0.75mm (presence of ulceration, regression, mitoses and Clark levels IV/V). Two groups were defined based on Breslow: (A) < or =1.00mm - major group with 17 patients; (B) 0.76-1.00mm - subgroup of 5 patients at threshold for sentinel biopsy. Both groups were compared with Breslow > 1.00 patients as Control Group, using Fischer's test. High risk of recurrence characteristics were reviewed in patients with Breslow <0.76mm and expressed as percentages. Results: Sentinel lymph node biopsies were positive in 40,5% (15/37) of melanomas with Breslow >1.00mm. In patients with Breslow < or =1.00mm (A) there was 5.8% (1/17) sentinel node positivity. In the subgroup of patients with Breslow 0.76-1.00mm (B) sentinel nodes were positive in 20% (1/5). When testing statistically, Group A (< or =1.00mm) was different from Control group patients (> 1.00mm) regarding sentinel node positivity (p=0.008), while Group B (0.75-1.00 mm) was similar to Control group patients (p=0.35). In patients with Breslow <0.76 mm with high risk characteristics on pathologic report, ulceration was not present in any patient, 16,7% were Clark levels IV/V, mitoses were present in 70% of patients, lesions were in vertical phase of growth in 40% and regression was present in 36%. Conclusions: 1. Sentinel node biopsy in melanomas with Breslow 0.76-1.00mm should be routinely indicated due to a high positivity rate (20% in our sample) in this range. 2. Node positivity in patients with Breslow <0.76mm (5.8%) was statistically different from node positivity in Breslow >1.00mm group (40%; p=0.008) rising the question that indication of sentinel node biopsy in Breslow <0.76mm is controversial.

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Utility of Routine PET/CT for Initial Staging of Patients with Sentinel Lymph Node Positive Melanoma J.J. Baker,[1]* N.A. Newman,[2] E.A. Levine,[2] A.M. Deal,[1] J.S. Frank,[1] J.H. Stewart,[2] P. Shen,[2] M.O. Meyers.[1] *1. Surgical Oncology, University of North Carolina, Chapel Hill, NC; 2. Wake Forest Baptist Medical Center, Winston-Salem, NC.*

Background: It is unclear if the routine use of Positron Emission Tomography /Computed Tomography (PET/CT) to stage patients with sentinel lymph node (SLN) positive stage III melanoma at the time of diagnosis has utility. We evaluated the likelihood of routine PET/CT to detect occult metastatic disease in this population. Methods: Two IRB-approved, cutaneous melanoma databases were queried to identify SLN positive stage III patients who had PET/CT as part of their initial staging workup. Associations with a positive PET/CT were evaluated using Fisher's exact test. Positive (PPV) and negative (NPV) predictive values of PET/CT were also determined. Results: 146 patients had a positive SLN and were staged with PET/CT. There were 82 men and 64 women. Median age was 55 years. Median Breslow depth was 2.6mm. 15 patients were T1, 37 T2, 47 T3, 41 T4 and 6 unknown. 58 were ulcerated and 52 had a mitotic rate >1. PET/CT was interpreted as suspicious for metastasis in 13 patients (8.9%) and negative in 133 (91.1%). 7 (4.5%) of the suspicious PET/CT scans were subsequently proven to be negative for malignancy and 2 (1.3%) proved to be an incidental cancer; one thyroid and one B-cell lymphoma. 4 patients (2.7%) were found to have asymptomatic metastatic melanoma (one clinically unsuspected in transit metastasis, two lung nodules and one bone lesion). PPV was 31% and NPV 100% for PET/CT. No demographic or pathologic factors were associated with the likelihood of a positive PET/CT. Conclusions: Patients with SLN positive melanoma are unlikely to have asymptomatic occult metastatic disease detected by PET/CT at the time of diagnosis. However, given that we now have effective systemic agents for stage IV melanoma patients, future research should be directed toward identifying groups at highest risk for occult metastatic disease in whom serial PET/CT imaging might offer the greatest yield.

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Assessment of Opto-Electronic Volumetry and Manual Perimetry on the Diagnosis of Lymphedema L.L. Campanholi,[1]* J.P. Duprat,[1] J.T. Fregnani.[2] *1. AC Camargo Hospital, Sao Paulo, Sao Paulo, Brazil; 2. Barretos Cancer Hospital, Barretos, Sao Paulo, Brazil.*

INTRODUCTION: The opto-electronic volumetry is a newer method that has been considered as the new gold standard for diagnosis of lymphedema, but has been little studied because of its high cost. The objective is to evaluate a method of diagnosing lymphedema of limbs, in patients with radical lymphonodectomy as a treatment for cutaneous melanoma. METHODS: Study participants were 43 patients who underwent lymphonodectomy between 1990 and 2008. We excluded patients with amputation of a limb or bilateral dissection. The measurement of the limbs was made by opto-electronic volumetry (Perometer) and manual perimetry applied in the formula of truncated cone. The adherence to normality was verified by the Kolmogorov-Smirnov Test and Shapiro-Wilk Test. The difference between the volumes of manual perimetry and opto-electronic volumetry was verified by Wilcoxon test. SPSS 15.0 for Windows was used to perform statistical tests. RESULTS: We studied 43 patients: 17 with axillary lymphonodectomy (39.5%), 12 with inguinal (27.9%) and 14 with ilio-inguinal (32.6%). Women were majority (62.8%) and lymphonodectomy was more common in the left limb (58.1%). The rate of lymphedema by upper limb in opto-electronic volumetry was 47.1% and 69.2% in lower limb; in manual perimetry, 47.1% and 61.5% respectively. Mean difference in volume between the upper limbs in perimetry was - 2,2 ml (right to left limb) and in opto-eletronic volumetry was – 45,8ml, but in the lower limbs, the mean difference was 491.3 in perimetry and 453,3 in opto-eletronic volumetry. There was a difference in volume in upper limbs compared measurement techniques (p= 0.028). In lower limbs, the measurements were consistent (p= 0.469). CONCLUSIONS: Perometer provides a more accurate measurement, practical, and fast. Study participants prefer Perometer, because the comfort and practicality in the assessment. Perometer diagnosed lymphedema that went unnoticed by manual perimetry in the lower limb.

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Mitf Expression in Malignant Melanoma Predicts Occult Lymph Node Metastases L. Ailabouni, G.I. Salti.* *Surgical Oncology, Univ Illinois, Chicago, IL.*

Background: Micropthalmia transcription factor (Mitf) is involved in melanocyte development and differentiation. We previously reported that Mitf expression, as detected by immunocytochemistry, is an independent prognostic marker in patients with melanoma. However, the clinical significance of Mitf expression in melanoma is unclear. Methods: We examined primary cutaneous melanomas from 151 patients undergoing nodal staging. We quantified the percentage of tumor cells whose nuclei stained by Mitf antibody visually. Correlation between Mitf expression and nodal status was evaluated by the Mann-Whitney U test. Results: Patient whose melanomas expressed Mitf had a significantly improved overall survival (P=0.001). In addition, Mitf ≤50% was expressed in 42/51 (82%) primary tumors from patients with pathologically positive lymph. Moreover, Mitf >50% was expressed in 46/100 patients with negative lymph nodes. These results are statistically significant (P=0.015). Conclusion: Our study shows a correlation between expression of a molecular marker in the primary cutaneous melanoma and likelihood of regional lymph node metastases. Mitf immunostaining of ≤50% reliably predicts patients most likely to harbor occult lymph node metastases.

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Risk and Location of Additional Cervical Lymph Node Involvement in Melanoma Patients with a Positive Cervical Sentinel Lymph Node Biopsy J.R. Hyngstrom,* J.M. Gardner, K.A. Delman, MD, A. Yang, MD, C.W. Schacherer, J.N. Cormier, MD, MPH, J.E. Gershenwald, MD, P.F. Mansfield, MD, A. Lucci, MD, R. Royal, MD, V. Prieto, MD, M.I. Ross, MD, J.E. Lee, MD. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Introduction: Primary tumor and sentinel lymph node (SLN) features which predict the presence of additional nodal disease in patients with a positive SLN biopsy (B) have been identified for the overall group of melanoma patients as a whole. It is unclear whether the same features can be used to guide management of the subset of melanomas with cervical SLN drainage. The purpose of this study was to determine the frequency, anatomic level, and clinicopathologic features predictive of additional cervical nodal metastases in melanoma patients with a positive cervical SLNB. Methods: A single institution melanoma patient database was retrospectively queried to identify all patients who had a positive cervical SLNB and then underwent a comprehensive neck dissection (CND) levels I/II-V between 1996 and 2009. Patient demographics, pathology, operative, and anatomic details were analyzed. Results: 39 patients underwent CND after a positive SLNB. The median number of SLNs harvested was 3(range 1-7). Five (13%) patients had >1 positive SLN, including 2(5%) who had >1 level with positive SLNs. Four (10%) patients had additional nodal disease at CND. Univariate analysis of primary tumor/lymph node characteristics identified Breslow thickness, lymphovascular invasion, and multiple positive SLNs as predictors of additional nodal disease. (Table) While disease was limited to the single anatomic level identified by SLNB in 37(95%) patients, 2(50%) of the 4 patients with additional nodal involvement had disease outside the SLNB level at CND. Conclusion: Additional cervical nodal disease after a positive SLNB is infrequent, particularly when only one SLN is positive, but when present frequently involves anatomic levels adjacent to or remote from the anatomic level defined by SLNB. Multilevel cervical disease was more common in patients with multiple positive SLNs and was associated with a higher risk of additional nodal disease. These data suggest a continued role for CND in patients with positive cervical SLNB, but justify prospective studies to explore the role of selective dissection or observation in patients with solitary SLN metastases.

Predictors of Additional Cervical Nodal Involvement

Descriptive variables	p value
Primary tumor ulceration	1.0
Breslow > 2mm	**0.05**
LVI	**0.02**
SLN Extracapsular extension	0.2
Multiple positive SLN	**0.07**
≥ 1 SLN harvested	1.0

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The Impact of Ulceration on Sentinel Node Biopsy in Acral Lentiginous Melanoma (ALM): An Ideal Population for Adjuvant Therapy? H. Martínez Saíd,* M. Cuellar, R. Salcedo, V. Villavicencio, A. Padilla-Rosciano, A. Mohar-Betancourt. *Instituto Nacional de Cancerología, Mexico City, Mexico.*

INTRODUCTION: Patient with ulcerated melanomas and metastasis limited to sentinel node seems to be the ideal group for adjuvant therapy with pegylated interferon. We present our experience with sentinel node biopsy in acral lentiginous melanoma. METHODS: We review our prospective database of melanoma to analyze the frequency of ulceration and it's relation to sentinel node biopsy. RESULTS: During the period of January 2003 to December of 2008, 458 patients with melanoma a sentinel node biopsy was done, there were 232 patients with ALM. 139 female patients (60%) and 93 male patients were included. The median age was 55.7 years (20 to 92 years), with 58.3% (134 patients) were younger than 60 years. The patient distribution according to T was: Tis with one (0.5%), T1 12(5.9%), T2 61 (30%), T3 45 (22%), and T4 84 (41.4%) with 0%, 8.3%, 18%, 46.7 and 69% of ulcerated melanoma respectively. 26.1% of all patients have a positive sentinel node and complementary lymph node dissection (CLND) was done. In 23.5% of cases other than SN was found with metastases. For the population with negative SN was maintained in observation. The recurrence rate for the patients with positive sentinel node was 47.54% vs 17.33% in the negative SN group (p=0.001). 58.3% of positive CLND vs 44.4% of negative CLND (p=0.00014). The main site of recurrence for patients with positive CLND was distant metastases in 71%, versus 44% of negative CLND (p=0.0003) an 11% of negative SN (p=0.00004). The mean Breslow thickness for positive SN and ulcerated melanomas was 5.4 mm vs 3.2 of negative SN and was no significative. (p=0.19); gender, age and subsite of melanoma there were also no significant The main predictive factor for positivity of SN was ulceration (RR 1.38 (1.1491 – 1.6716) p=0.0001) CONCLUSION: The incidence of ulcerated melanomas and positive sentinel node in ALM is higher than reported in other subtypes.

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Evidence in Support of a Better Nodal Staging System for Melanoma: The Clinical Relevance of Metastatic Disease Confined to the Sentinel Lymph Nodes D.S. Reintgen,[1]* M.T. Reintgen,[1] L. Murray,[1] K. Akman,[1] R. Giuliano,[2] S. Shivers.[1] *1. Surgery, University of South Florida, Tampa, FL; 2. Helen Ellis/USF Cancer Program, Tarpon Springs, FL.*

Introduction: The hypothesis tested in this study was whether patients with Stage III metastatic melanoma confined to their sentinel lymph nodes (SLN) had a better disease-free (DFS) and overall survival (OS) than patients who had SLN and non- sentinel lymph node (NSLN) metastases. Methods: 463 patients were extracted from a prospective database who had known primary melanoma and regional nodal disease (Stage III). Patients were identified who were clinically negative in their regional basin but with lymphatic mapping were found to have positive SLNs and subsequently underwent a complete lymph node dissection. Total number of SLN and NSLN were obtained. 62.4% of the population had SLN only disease while 174 patients had SLN and higher echelon nodes involved. Results: For patients with a total of 2 nodes positive, those with disease confined to the SLNs had a significantly better prognosis (DFS and OS: $p < 0.00001$) than if one SLN and one non-SLN was involved. This difference was apparent for those patients with a total of 3 nodes positive and 4 or more node positive in their regional basin. As the regional metastatic disease overwhelms the SLNs and involves NSLNs disease free and overall survival decreases. Conclusion: Prognosis in melanoma patients with microscopic Stage III disease is dictated by number of nodes positive according to the current AJCC staging system. However if the metastatic disease is confined to the SLNs, prognosis is improved regardless of total number of nodes involved. Once the metastatic disease overwhelms the SLN and involves NSLNs the biologic behavior changes to portend a worse survival. These data make an argument that the current N-staging system for melanoma should be changed to incorporate SLN vs. NSLN involvement.

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An Assessment of the Value and Relevance of Current Quality of Life Tools for Post-surgical Patients Treated for Cutaneous Melanoma N. Patel,[1] A. Ayub,[1] K. Fung,[2] J.J. Garioch,[3] M. Moncrieff.[1]* *1. Plastic & Reconstructive Surgery, Norfolk & Norwich University Hospital, Norwich, Norfolk, United Kingdom; 2. University of East Anglia, Norwich, Norfolk, United Kingdom; 3. Norfok & Norwich University Hospital - Department of Dermatology, Norwich, Norfolk, United Kingdom.*

AIM: The aim of this study was to assess the relevance of both generic (EORTC QLQ-C30) and specific (FACT-M) quality of life (QOL) instruments for surgical melanoma patients. METHOD: 357 questionnaires were sent to patients who had undergone wide local excision and sentinel lymph node biopsy in a large UK teaching hospital from 2008-2011 and the responses were analysed. RESULTS: 206 (58%) questionnaires were returned: 103 men and 103 women, median age was 62 yrs (range 25-84 yrs). There were no consistent differences in the sub-domains of the FACT-M scores when analysed across sex and location of primary (axial v. extremity). Increasing AJCC stage showed worsening FACT-M subscale scores with the exception of emotional well-being and functional well-being, where there was no significant difference. Melanoma surgery scale scores were worse for extremity lesions (p=0.031) and increasing AJCC stage (p=0.016). There were no consistent differences in the subdomains of the EORTC QLQ-C30 questionnaire when analysed across sex, location of primary (axial v. extremity) and AJCC stage (I-III). There was no significant difference in global quality of life scores and, in contrast to the

FACT-M study, pain scores were only different across AJCC stage (p=0.034). Of the 30 questions within the QLQ-C30, an average of 70.3% felt the questions related to their condition. Overall, only 62% of patients felt that this questionnaire was 'quite a bit' to 'very much' relevant to their melanoma. CONCLUSION: QOL end-points are increasingly regarded as obligatory for major trials measuring treatment outcomes. We conclude that the FACT-M questionnaire lacked discrimination for measuring emotional, social and functional well-being for surgical patients and the EORTC QLQ-C30 lacked any discrimination for surgical patients and/or melanoma patients. Our results would suggest that a more robust melanoma-specific tool is required for investigating QOL outcomes after surgery for cutaneous melanoma.

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Merkel Cell Carcinoma of Unknown Origin: A Better Prognosis?
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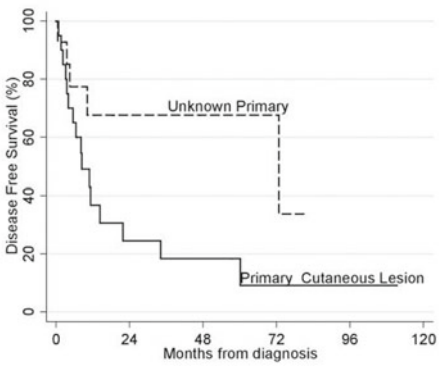
Introduction: Merkel cell carcinoma (MCC) is a cutaneous malignancy with poor prognosis, with a high rate of regional and metastatic disease. MCC arising from a nodal basin without evidence of a primary cutaneous site has been described, but clinical significance is not clear. We present our experience at a tertiary care referral center with stage III MCC, with and without known primary cutaneous (PC) site. Methods: 35 patients with stage III MCC were identified from our tumor registry between 1996 and 2011. Data regarding demographics, tumor stage, surgical and chemoradiation treatment, and clinicopathological outcomes were analyzed, with the primary endpoints being disease-free and overall survival (DFS and OS). Kaplan-Meier analysis was used to estimate median DFS and OS. Results: 15 patients presented with nodal MCC with an unknown primary (UP) site, while 20 patients presented with a primary cutaneous (PC) with nodal metastasis, all consistent with stage III MCC. For patients with UP vs. PC, nodal basins included cervical (48% vs. 20%), axilla (13% vs. 40%), and inguinal (40% vs. 40%). There was no significant difference in median age of presentation or gender ratio for UP vs. PC (66 years vs. 71 years and 70% male vs. 65% male). Median follow-up time for UP vs. PC was 17 vs. 11 months. Treatment strategies varied with a combination of regional lymphadenectomy, radiation, and chemotherapy. Of patients with UP vs. PC, 20% vs. 45% underwent a combination of regional lymphadenectomy and radiation (median total RT dose: 5940 Gy vs. 4550 Gy), whereas an additional 30% vs. 20% had chemotherapy added to their regimen. Median DFS for UP was 72 months compared to 8 months for PC (HR=0.36, p=0.04). Median OS for UP was 73 months compared to 17 months for PC (HR=0.47, p=0.15). Conclusion: MCC with unknown primary site appears to portend a better prognosis than Stage III MCC with a cutaneous primary. In patients with UP, a trend towards increased median OS was observed, while median DFS was significantly improved



P281

Incorporating the Keystone Flap to Close Skin/Soft Tissue Defects of Cutaneous Melanoma Excisions J.J. Baker,* A.M. Deal, M.O. Meyers, J.S. Frank, D.W. Ollila. *University of North Carolina, Chapel Hill, NC.*

Introduction: The keystone flap (KF), fasciocutaneous island perforator flap, has been used to close defects after wide local excision of melanoma (WLE), reportedly decreasing the need for skin graft closures. We examined our method of closure before/after incorporating KF into our practice. Methods: A prospective IRB-approved database of cutaneous melanoma patients treated from 2007-2011 was used to identify patients who underwent a WLE. Patients with tumors of face/scalp, hands and digits were excluded. We calculated square area (cm^2) of the excision defect based on measurements in the operative/pathology report. The KF was performed as described by Moncrieff et al., ASO 2008. Associations were evaluated using Fisher's Exact tests. Results: We identified 350 eligible patients, mean age 55 years (range 19-60). 138 patients prior to/212 after incorporating the KF in June 2008. Tumor location: 95 (27%) upper extremity, 28 (8%) shoulder, 154 (44%) trunk, 56 (16%) lower extremity, 17 (5%) foot. Mean Breslow thickness: 1.5mm (range 0.12mm-13.5mm). Mean area of defect 18.6 cm^2 (range 1.1-141.3cm^2). 205 (58%) tissue rearrangement flaps (TRF) (36 (10%) were KF), 77 (22%) primary closure, 46 (13%) skin graft (15 FTSG, 31 STSG), 14 (4%) closure by secondary intention (SI), 8 (2%) a combination. Since incorporating KFs, the total percentage of skin grafts has not changed (15% v 12%, p=0.4). However, the percentage of skin grafts done for defects 10-20cm^2 has significantly decreased since the addition of KF (22% v 7%, p=0.03). For defects <10cm^2 or ≥20cm^2 incorporation of KF did not alter the need for skin grafts (Table 1). Conclusion: This is the first dataset to quantify the reduction of skin grafts once KF closures are incorporated into a melanoma practice. The KF has decreased the percentage of skin grafts needed in the intermediate size defect group but does not supplant the need to cover large skin defects. These data may be useful in discussing anticipated closure with melanoma patients preoperatively.

Size of Defect		Primary	TRF	KF	Skin Graft	SI	Combo
Pre June 2008	<10cm^2	14 (24%)	39 (68%)	0	4 (8%)	0	0
	10-20cm^2	4 (10%)	27 (65%)	0	9 (22%)	1 (3%)	0
	≥20cm^2	5 (12.5%)	26 (65%)	0	8 (20%)	0	1 (2.5%)
Post June 2008	<10cm^2	18 (28%)	27 (41%)	6 (9%)	7 (11%)	5 (8%)	2 (3%)
	10-20cm^2	22 (25%)	25 (33%)	19 (25%)	5 (7%)	4 (5%)	2 (3%)
	≥20cm^2	16 (22%)	25 (35%)	11 (15%)	13 (18%)	4 (6%)	3 (4%)

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Single Institution Outcome Experience using Human Acellular Dermal Matrix as Temporary Coverage or Definitive Reconstruction for Cutaneous and Soft Tissue Malignancy Defects J.L. Deneve,* K.K. Turaga, S.S. Marzban, A.A. Sarnaik, R.J. Gonzalez, V.K. Sondak, J.S. Zager. *Surgical Oncology, Moffitt Cancer Center, Tampa, FL.*

Introduction: Definitive reconstruction after excision of skin and soft tissue malignancies (SSM) is sometimes delayed pending permanent margin analysis. Acellular dermis (AlloDerm®) reconstruction offers an excellent coverage alternative while awaiting negative margin assessment. We describe our experience using AlloDerm for temporary and permanent coverage of SSM defects. Methods: An IRB approved review of patients (pts) with SSM undergoing reconstruction with AlloDerm from 2007-2011 was performed. Clinicopathologic variables, early post-operative findings and subjective final cosmetic outcome were analyzed. Results: Sixty pts underwent resection with AlloDerm reconstruction with a median age of 72 years (33-92 years). Melanoma (70%) was the most frequent diagnosis. The median defect size was 44 cm2 (2-340 cm2), involving the lower extremity in 45% and scalp in 32%. AlloDerm was initially intended for use as a temporary biologic dressing in 68% (41/60) and permanent coverage in 19 (32%). Of the planned temporary coverage pts, 59% (24/41) underwent delayed skin grafting (SG), 10% (4/41) had delayed flap coverage. The remaining 31% (13/41) were managed by leaving the AlloDerm in place permanently without further reconstruction. In total, AlloDerm was used as a permanent dressing in 32pts (19 intended plus 13 unintended). Radiation was administered to 18 pts (30%) after AlloDerm reconstruction. Of these pts, 5 had AlloDerm loss, 3 of which underwent salvage SG and 2 healed by secondary intention. At first post-operative examination (5-10 post surgery), 83% had evidence of healthy AlloDerm graft incorporation. Complications were minor and self-limiting, most frequently cellulitis (15%) which responded to oral antibiotics in all cases. Conclusions: AlloDerm reconstruction after SSM resection offers a suitable coverage alternative. AlloDerm may serve as a bridge to permanent reconstruction with SG or even as a permanent biologic dressing of complex surgical defects with excellent early

cosmetic outcomes. In situations where adjuvant radiation is needed, AlloDerm can be used without major complications.

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Millennium 2238-Proteasome Inhibition is Effective in Malignant Melanoma E. Luedke,* W.E. Carson III. *Ohio State University, Columbus, OH.*

MLN2238 is a novel antitumor compound that specifically and reversibly inhibits the 20S proteasome. We hypothesized that the treatment of melanoma tumor cells with MLN2238 would enhance tumor cell apoptosis. Human melanoma tumor cells (A375, MeWo, CHL 1) were treated for 48h with various doses of MLN2238 (5 nM - 105 nM). Analysis of apoptosis was subsequently performed via Annexin V/propidium iodide staining. Time course experiments were performed at 12, 24 and 48h using the optimal dose of MLN2238. The combination of MLN2238 and interferon (IFN) alpha, sorafenib (a multikinase inhibitor), or PLX-4720 (a B-raf inhibitor) on melanoma cell apoptosis was evaluated in a similar fashion. IFN alpha dose = 100,000 U/mL. Sorafenib dose = 1 uM. PLX-4720 dose = 1-10 uM. MLN2238 dose response experiments performed on the A375 cell line delineated an optimum in vitro treatment dose of 35 nmol. Treatment of melanoma tumor cell lines for 48h with MLN2238 resulted in 64.5% cell death on average as compared to 13.4% observed in cells treated with PBS control ($p<0.0001$). Similar results were obtained with the MeWo and CHL-1 cell lines. Time course experiments conducted in the A375 cell line revealed that apoptosis began between 12-24h and reached maximal levels at 48h. The combination of MLN2238 and IFN alpha resulted in an average cell death of 79.1%, as compared to 64.9% for MLN2238 alone and 17.1% for IFN alpha alone. The addition of sorafenib to MLN2238 treatment resulted in 82.9% cell death as compared to 64.1% for MLN2238 treatment alone and 12.8% for sorafenib treatment alone. The addition of 1uM PLX-4720 to MLN2238 treatment resulted in 29.2% cell death as compared to 25.2% for MLN2238 treatment alone. MLN2238 and MLN2238 combination therapy had no adverse effects on normal cells including normal human lymphocytes. MLN2238 is a novel proteasome inhibitor with direct antitumor activity. MLN2238 in combination with IFN alpha or other targeted agents should be examined further as a potential therapy in melanoma.

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IL-27 Inhibits Proliferation and Promotes Apoptosis of the SK-MEL-5 Melanoma Cell Line Y. Fang, E.J. Herrick, M.B. Nicholl.* *Surgery, University of Missouri, Columbia, MO.*

IL-27, a member of the IL-12 cytokine family, promotes antitumor immune response through the TH1 pathway. In addition, a direct effect on growth of several human melanoma cell lines has been reported. The mechanisms of tumor growth inhibition are not well studied and the effect of IL-27 on growth of a widely used melanoma cell line SK-MEL-5 has not been investigated yet. In this study, we investigated the direct effect of IL-27 on proliferation and apoptosis of SK-MEL-5 cells and the molecular mechanisms governing these findings. Clonogenic survival assay, immunohistochemistry (IHC), TUNEL staining, proliferation and caspase-3 activity kits were used to evaluate the effects of IL-27 on cell survival, proliferation and apoptosis. The percentage of colonies, PCNA+ cells and the OD value of SK-Mel-5 cells were significantly decreased in the presence of IL-27, and TUNEL+ cells and the relative caspase-3 activity were both increased in the presence of IL-27. RT-PCR and IHC were further used to investigate the underlying molecular mechanisms. The anti-proliferative effect of IL-27 correlated with decreased expression of cyclin B, cyclin D, cyclin E and cdk2 and its pro-apoptotic effect correlated with decreased expression of FLIP and survivin. Thus, IL-27 inhibits proliferation and promotes apoptosis of the SK-MEL-5 melanoma cell line by modulation of pro- and anti-proliferative molecules as well as pro- and anti-apoptotic molecules. Our study supports previous findings suggesting IL-27 has a direct antitumor effect.

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Natural History of Merkel Cell Carcinoma Following Locoregional Recurrence T.E. Grotz,* T.I. Tarantola, C.C. Otley, A.L. Weaver, M.E. Mc Gee, J.W. Jakub. *Mayo Clinic, Rochester, MN.*

Background: Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine malignancy with a propensity for locoregional recurrence. Because of its infrequent nature little is known regarding the natural history of MCC following locoregional recurrence. Methods: A retrospective review of patients with MCC diagnosed at three clinic sites from 1981-2008. For each outcome (subsequent locoregional recurrence, distant recurrence and death), the survival-free of the outcome was estimated using the Kaplan-Meier method. Associations of patient and clinical characteristics with the outcomes were assessed by fitting Cox proportional hazards regression models and summarized by calculating hazard ratios (HR) and corresponding 95% confidence intervals (CI). Results: Among the 240 patients diagnosed with MCC, 70 (29%) patients were identified who developed locoregional recurrence as the first site of recurrence. The median time from diagnosis to locoregional recurrence was 6 months. The pattern of first locoregional failure in this group includes 25 (36%) local, 18 (26%) in-transit and 27 (38%) nodal recurrences. Recurrences were most commonly treated by surgery and radiation. Three years after the initial recurrence, locoregional control was 75% and the survival-free of distant recurrence was 56%. Locoregional recurrence is associated with a 3-year overall survival of 39% but was significantly improved with radiation therapy ($p < 0.001$). In-transit recurrences had a higher propensity for subsequent locoregional recurrences (HR: 3.04, 95% CI: 0.85-10.95; $p = 0.047$), while nodal recurrences had a higher propensity for distant recurrence (adjusted HR: 9.49, 95% CI: 2.82-31.89; $p < 0.001$). Nodal status at time of original surgery and time to first recurrences were important predictors of distant recurrence ($p < 0.006$) and overall survival following locoregional recurrence ($p < 0.001$). Conclusion: Locoregional recurrence is a substantial problem in patients with MCC and is a poor prognostic sign. In those patients who experience a locoregional recurrence, aggressive efforts to regain locoregional control appear warranted and may result in long-term survival.

Table I. Factors evaluated for an association with death due to any cause

Characteristic	Univariate Cox regression analysis		Multivariable Cox regression analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age		0.001		0.008
≤ median	Referent		Referent	
> median	2.79 (1.49, 5.21)		2.61 (1.29, 5.27)	
Sex		0.16		
Male	Referent			
Female	0.58 (0.28, 1.23)			
Size of primary		0.24		
≤ 2 cm	Referent			
> 2 cm	0.59 (0.25, 1.41)			
Location of primary		0.048		
Extremeties	Referent			
Head/neck	2.25 (1.14, 4.45)			
Trunk/buttocks	2.11 (0.92, 4.83)			
Original nodal status		<0.001		<0.001
None removed	Referent		Referent	
Nodes removed, all negative	0.84 (0.35, 2.01)		1.62 (0.65, 4.05)	
Nodes removed, at least 1 positive	4.47 (2.25, 8.88)		5.49 (2.42, 12.47)	
Radiation treatment of locoregional recurrence		0.003		<0.001
No	Referent		Referent	
Yes	0.40 (0.22, 0.73)		0.21 (0.10, 0.42)	
Type of first recurrence		0.24		
Local	Referent			
In-transit	1.72 (0.83, 3.56)			
Nodal	0.98 (0.48, 2.03)			
Disease-free interval from primary surgery to first recurrence (years)*	0.62 (0.49, 0.79)	<0.001	0.68 (0.54, 0.86)	0.001

* HR per doubling in duration from primary surgery to first recurrence.

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Impact of Sentinel Lymph Node Status on Prognosis of Thick Cutaneous Melanoma M. Everett,[1]* R. Gutman,[2] H. Gutman.[3] *1. Department of Surgery, Nassau University Medical Center, East Meadow, NY; 2. Brown University, Providence, RI; 3. Rabin Medical Center, Beilinson Hospital, Sackler Faculty of Medicine, Petah Tiqwa, Israel.*

Introduction:Melanomas ≥ 4mm have been considered as high risk for occult metastasis at presentation. Sentinel lymph node biopsy (SLNB) has

generated subgroups of thick melanomas with SLNB- or with micro-metastases. Comparing the outcomes and patterns of failure of these subgroups may identify those with better prognosis, as with thinner melanomas. Methods:Retrospective analysis of prospectively maintained single institution database from 1/1994-12/2010. Group 1 had SLNB+ and completion lymph node dissection (CLND), Group 2 had SLNB-, and Group 3 had SLNB+ but did not undergo CLND. Demographics, tumor characteristics and outcomes were noted. Recurrence was defined as presentation of melanoma after SLNB ± CLND, categorized as either locoregional lymphatic, distant or both. Differences for continuous variables were analyzed by Kruskal-Wallis test and Fisher test for proportions. Survival curves were compared by the G-rho family of tests. Cox Proportional Hazards model was applied to examine difference in hazard of recurrence across groups. Results: 131 patients (Table) with melanoma ≥4mm underwent excision + SLNB, median follow-up time 33.3 months (range 0.8-239.3). Overall recurrence rate was 35.8% (47); 40% (17), 31% (24), 50% (6) for Groups 1, 2, 3, respectively. Median time to recurrence was 365 days (132-1136), 529 (47-2175), 426 (256-1644) for Groups 1, 2,3. Group 1 experienced 21% (9) lymphatic metastases vs. 9% (7) for Group 2(p=0.15). Distant metastases occurred in 17% (7) of Group 1 and 19%(15) in Group 2. Disease-free survival (DFS) was longer and hazard ratio lower for Group 2 vs. Group 1(HR 0.58, p=0.089). Melanoma-specific survival was longer for Group 2 vs Group 1(p=0.0074, HR 0.4, p=0.01). Furthermore, 7 Group 2 patients suffered locoregional failures; 3 of these 7 are false negative SLNB, thus should be moved from Group 2 to Group 3, further reducing the regional failure rate in Group 2. Conclusion: Our findings of 41% SLNB+ at diagnosis and 40% SLNB+, 31% SLNB- recurrence rates are comparable to current literature. We demonstrate SLNB- is associated with a trend for fewer locoregional recurrences and support existing data for longer DFS and melanoma-specific survival.

Demographics and Tumor Biology

	Group 1	Group 2	Group 3	Total	Percent Total
N	42	77	12	131	
Male	27	42	8	77	58.77
Female	15	35	4	54	41.22
Acral	5	9	2	16	12.21
Ulceration	31	45	6	82	62.59
Regression	11	5	1	17	12.97
Satelites	6	3	1	10	7.6
Breslow Med	5.5 (4-25)	5.5 (4-13)	6 (4.2-45)	5.5 (4-45)	
Breslow Mean	6.717	6	10.333	6.793	
Clark Median	4 (3-5)	4 (3-5)	5 (4-5)	4	
Location of Primary					
Trunk	22	23	7	52	39.69
Extremity	14	40	5	59	45.03
H&N	6	14	0	20	15.26

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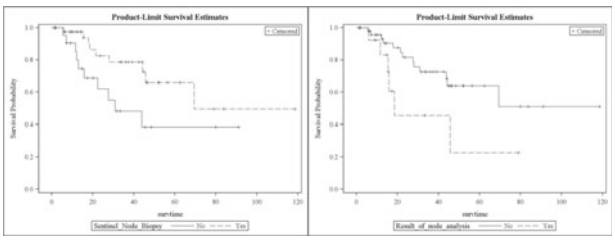
Sentinel Lymph Node Biopsy in Merkel Cell Carcinoma of the Skin: A Mortality Benefit? G.B. Deutsch,* S. Anantha Sathyanarayana, M. Beg, A. Kadison, J.L. Ricci, J.D. Sullivan, J. Wang, R. Zaidi, C.C. Conte. *North Shore University Hospital, Hofstra-NSLIJ School of Medicine, Manhasset, NY.*

Introduction Merkel cell carcinoma (MCC) is a relatively rare yet aggressive cutaneous neoplasm with an approximate incidence of 0.3 cases per 100,000 individuals. As disease prevalence has increased more cases are being treated at non-cancer specialty hospitals. We report our experience with the management of MCC, specifically related to the utilization of sentinel lymph node biopsy (SLNB). Methods A retrospective review was performed of 65 subjects with a final pathologic diagnosis of Merkel cell carcinoma. All patients underwent surgical resection between January 2001 and December 2010. Data was collected from both the institutional tumor registry and patient charts. Tumor size and staging, microscopic and gross margins, lymphovascular invasion (LVI), and the result of SLNB and/or lymph node dissection (if performed) were used as separate stratification variables for survival estimates. Results The average age of our population at diagnosis was 77.2 years of age. The anatomical location of our cases was as follows: 58% extremities, 32% face, and 10% trunk. The AJCC 6 staging breakdown: Stage I 55.7%, Stage II 13.5%, Stage III 25.0%, and Stage IV 5.8%. Overall five-year survival for the study population was 54%. The presence of positive microscopic margins (15.6%) was a predictor of mortality (p<0.0001), whereas LVI was not significantly associated with mortality (p<0.1062). 63.5% of patients underwent a SLNB and 23.8% had a regional lymph node dissection. Those that underwent SLNB had a significantly higher five-year survival than those who did not (69.4% vs. 30.9%; p<0.0416). After controlling for stage and tumor location there was no change in the observed survival benefit (p<0.5502 and p<0.5293, respectively). Of those that had a SLNB, a positive result was associated with a higher mortality (p<0.0435). Regional lymph node dissection did not lead to improved outcomes. Conclusions In our study, performing SLNB in patients with Merkel cell carcinoma was associated with a decreased mortality. Further therapy in the form of completion node dissection did not improve that survival. A larger study group will be necessary to validate these findings.



Product-Limit Survival Estimates

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Role of Sentinel Node Biopsy in Thin and Thick melanoma E. Pennacchioli,[1]* N. Mozzillo,[2] C. Caracò,[2] G. Botti,[2] G. Viale,[1] F. Verrecchia,[1] A. Testori,[1] G. Tosti,[1] S. Gandini.[1] *1. Melanoma and Sarcoma Surgery, European Institute of Oncology, Milan, Italy; 2. Istituto dei Tumori G.Pascale, Napoli, Italy.*

Background: Sentinel node biopsy (SNB) is the standard procedure for staging of melanoma patients. Its role in thin (< 1 mm) and thick (> 4 mm) melanomas is still under discussion. Methods and Results: we conducted a retrospective analysis of patients with thin (490 cases) and thick (298 cases) melanomas undergone SNB. Concerning thin melanoma subgroup, the mean thickness is 0,80 mm and the SNB positive rate is 5%. 5yrs overall survival (OS) for patients with negative SLN is 98% and 5yrs OS for patients with positive SLN is 85%: the difference is statistically significant (P= 0.01). Concerning thick melanoma subgroup, the mean thickness is 6.6 mm and the SNB positive rate is 39.3.%; melanoma ulceration was not associated statistically with SLN status (63.5 in negative SLNs vs 67.5 in positive SLNs; P = 0.3); recurrence was detected in 82 of 181 patients (45.3%) with tumour negative SLNs vs 63 out of 117 (53.8%) of tumour positive SLNs (P= 0.1). Median primary tumour thickness had no effect on SLN status (5.0 mm in 181 negative SLNs vs 5.0 mm in 117 tumour positive SLNs P= 0.3). Our series show 47 % OS at 5 years in positive SLNs and 65.7% at 5 years in negative SLNs. As shown in the analysis of our data, the SNB technique is useful to provide reliable diagnostic and prognostic information also for melanoma patients with Breslow thickness ≤ 1 mm and > 4 mm. In thick melanomas it should be considered for completion lymph node dissection and adjuvant therapy.

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Prognostic Factors for Nodal Spread in Thin (≤1mm) Melanoma: A Meta Analysis A.N. Lundy,* K.E. Armeson, B. Hill, A.C. Parks, N.F. Esnaola, D.J. Cole, E.R. Camp. *Medical University of South Carolina, Charleston, SC.*

BACKGROUND: Although national guidelines recommend sentinel lymph node biopsy (SLNB) for T1b and greater melanomas, the procedure is controversial for thin (≤1 mm) tumors given the overall low rate of nodal spread. Several retrospective studies have identified possible pathologic predictors of SLN metastasis. We conducted a meta-analysis to determine the likelihood of association of these histologic variables with nodal spread in thin melanoma, in an effort to identify features that could be used to identify optimal candidates for SLNB. METHODS: We systematically searched PubMed and MEDLINE for studies (1992-2011) in which SLN biopsy was performed in patients with thin melanoma. Pathologic features of the primary tumor (Breslow thickness, Clark level, ulceration, regression, and mitotic rate) in both node-negative and node-positive patients were examined. Studies were combined using either fixed or random effect Mantel-Haenszel meta-analytic methods. Publication bias was assessed using rank correlation tests and funnel plots. Odds

ratios (OR) and summary estimates were calculated for each variable. RESULTS: Twenty studies (3202 patients) met the inclusion criteria; 171 patients (5.4%) overall had a positive sentinel node biopsy. The factors significantly associated with nodal spread were ulceration (OR 3.3; 95% CI 1.8-6.0), depth >0.75 mm (OR 2.4; 95% CI 1.5-3.8), and Clark level 4/5 (OR 1.8; 95% CI 1.3-2.6). The rate of SLN positivity in these groups was higher: 9.4% (ulceration), 7.7% (depth 0.75-1 mm), and 7.5% (Clark 4/5) . When tumor mitotic rate was classified as high vs. low rate, the OR for high mitotic rate was borderline significant (OR 3.1; 95% CI 1.0-9.7), with substantial heterogeneity across studies. Regression did not significantly correlate with sentinel node status in our analysis. CONCLUSIONS: Increased depth (>0.75 mm), Clark level 4 or 5, and ulceration in thin melanomas are associated with an increased likelihood of SLN positivity. Study heterogeneity precluded definitive analysis of the effect of mitotic rate. Thin melanoma patients with high risk pathologic features should be strongly considered for sentinel lymph node biopsy.

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Predicting Brain Metastases in Patients Treated for Primary or Locoregional Melanoma T.L. Frankel,[1]* G. Plitas,[1] Z. Bamboat,[1] C. Ariyan,[1] M.S. Sabel,[2] M.S. Brady.[1] *1. Memorial Sloan-Kettering Cancer Center, New York, NY; 2. University of Michigan, Ann Arbor, MI.*

Introduction: The brain is a common site of recurrence in melanoma patients. Unfortunately, this may present as a seizure, hemorrhage, or death. Predictors of brain metastases are lacking, and screening patients at high risk for recurrence in the absence of symptoms has been ineffective. We sought to identify demographic and pathologic predictors of brain metastases in patients with primary and locoregional melanoma to facilitate targeted screening. Methods: Review of prospectively maintained databases was performed to identify patients treated for local/regional melanoma at two tertiary care centers who later presented with brain metastasis as a component of their initial recurrence. 104 patients were identified and compared to 254 patients initially treated for local/regional melanoma who developed non-brain distant recurrence. Univariate analysis was performed using chi squared and Wilcoxon rank sum tests. Logistic regression was used to confirm significance. Results: Patients with brain metastases were younger (58 vs. 54 yrs, p=0.01) but did not differ in gender (male:68% in both groups) or site of disease (head and neck 13.1% vs 20.2%, p=0.29). Brain metastasis patients had thinner primaries with a median thickness of 2.3 mm vs. 3.2 mm (p=0.009) in patients without brain relapse. There were no other pathologic differences including ulceration (52% vs. 46%, p=0.45), mitoses (9 vs. 8, p=0.20) or histologic subtype between patients with brain and extracranial metastases, respectively. There were no statistically significant differences in regional disease rates including sentinel node or any regional lymph node involvement. On multivariate analysis, younger age and increasing thickness were associated with brain metastases (OR=1.10 p=0.04 and OR=1.04 p=0.02, respectively). Conclusions: Brain metastases from melanoma are difficult to predict and often present with devastating complications. Although similar studies have associated ulceration and head and neck location with the development of intracranial disease, our analysis, which is the largest to date, demonstrated that thinner primary and younger age were associated with brain recurrence.

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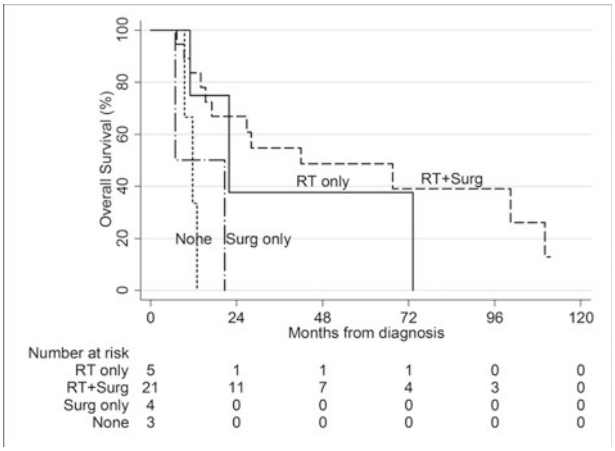
Optimal Treatment Approach for Lymph Node Metastases in Patients with Merkel Cell Carcinoma P. Papavasiliou,[1]* K.T. Chen,[1] R. Arrangoiz,[1] C.T. Murphy,[2] F. Zhu,[1] C. Perlis,[1] H. Wu,[1] A. Turaka,[1] J.M. Farma.[1] *1. Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. Temple University Medical Center, Philadelphia, PA.*

Introduction: The objective of this study was to compare outcomes of the different treatment modalities for lymph node metastases in patients with stage III MCC. Methods: A retrospective review of patients diagnosed with regional lymph node metastases from MCC was conducted. Outcomes including overall survival (OS) and disease free survival (DFS) were determined based on treatment modality of the affected regional lymph node basin. Results: Thirty-five patients diagnosed with regional lymph node metastases from MCC via sentinel lymph node biopsy (n=11) or clinically palpable lymph nodes (n=24) were reviewed. Median age was 69 years old (M:23, F:12). Treatment of the involved lymph node basin included radiation alone (n=5, median RT dose 54 Gy, range 45 to 60), lymphadenectomy alone (n=4), combined treatment (n=21, median RT dose: 47 Gy, range 31 to 60 Gy), or no treatment due to patient refusal (n=3). Median overall survival was 26.8 months. Median OS was 21.9 months for radiation alone, 11.9 months for lymphadenectomy alone, 41.9 months for combined treatment, and 6.8 months for patients who received no treatment to the involved nodal basin. There was a statistically significant difference in overall survival for combined treatment versus lymphadenectomy alone (p= 0.01). Median DFS was 13 months for radiation alone, 3.5 months for lymphadenectomy alone, 21.9 months for combined treatment, and 3.6 months for no treatment . There was a statistically significant difference in DFS for patients who had radiation alone versus lymphadenectomy alone (p= 0.04), and combined treatment versus lymphadenectomy alone (p= 0.02). Conclusion: The use of radiation either alone or in combination with lymphadenectomy demonstrated an improved OS and DFS compared with lymphadenectomy alone in the treatment of lymph node metastases from MCC. This study supports the use of adjuvant radiation therapy in the multidisciplinary care of patients with regional lymph node metastases from MCC.



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A Potential Role for Resveratrol as a Radiation Sensitizer for Melanoma Treatment Y. Fang, E.J. Herrick, M.B. Nicholl.* *Surgery, University of Missouri, Columbia, MO.*

Radiotherapy (XRT) is used to improve local control of melanoma and for palliation of metastatic disease. Clinical use of XRT for melanoma is often limited by extent of disease and the relative radioresistance of melanoma may limit the effectiveness of XRT. Our group and others have previously shown that resveratrol (RSV) enhances radiation sensitivity in radioresistant prostate cancer cell lines. In this study, the effect of XRT in combination with RSV on radioresistant melanoma line, SK-Mel-5, was evaluated by assessment of proliferation and apoptosis. Clonogenic assay, PCNA staining, Quick Cell Proliferation assay, TUNEL staining and caspase-3 activity assay were used to assess profileration and apoptosis, as appropriate. We found that the percentage of colonies of SK-Mel-5 cells, PCNA+ cells and the OD value of SK-Mel-5 cells were decreased after addition of RSV to XRT (XRT/RSV). TUNEL+ cells and the relative caspase-3 activity in SK-Mel-5 cells were increased after addition of RSV to XRT (XRT/RSV). We investigated the possible molecular mechanisms of decreased proliferation and increased apoptosis by using RT-PCR and immunohistochemical staining. The anti-proliferative effect of XRT/RSV correlated with decreased expression of pro-proliferative molecule cyclin B, cyclin D, cdk2 and cdk4. The pro-apoptotic effect of XRT/RSV correlated with decreased expression of the anti-apoptotic molecules FLIP, Bcl-2 and survivin. These data suggest that RSV enhances radiation sensitivity of SK-Mel-5 cells by inhibiting proliferation and promoting apoptosis. Resveratrol may have a potential role as a radiation sensitizer for melanoma treatment.

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Surgery in Stage IV Melanoma Patients: Results from a Single Institution E. Pennacchioli,* S. Gandini, F. Verrecchia, G. Tosti, G. Spadola, F. Baldini, M. Mosconi, P. Ferrucci, A. Testori. *Melanoma and Sarcoma Surgery, European Institute of Oncology, Milan, Italy.*

There is no consensus regarding the appropriate management of melanoma patients at stage IV and resectable metastases. Methods We conducted a sys-

tematic review and meta-analysis to examine the effect of surgery on overall survival (OS) in patients with resectable metastases. The systematic review was performed by searching MEDLINE, EMBASE, Cochrane and ISI Web of Science. The meta-analysis was performed using time-to-event data from which hazard ratios (HRs) and 95% confidence intervals (CIs) of OS were estimated and summary estimates were obtain through random effects model. Heterogeneity and publication bias were investigated by sensitivity analyses and funnel plot regression. Results Thirty-three retrospective studies evaluating survival from resected and unresected metastases were found from 1978 until 2010. In resected patients median follow-up is 1.5 years and 2-years OS is 27% whereas in unresected the median follow-up is 6 months and 2-y OS is 12%. Meta-analysis was carried out on the seven studies reporting information on visceral metastases and including 1,165 patients. We included also 93 patients at stage IV treated at the Institute. Surgery has shown an improvement in survival of patients managed with palliative resection of their visceral metastases: the summary estimate suggests a significant decrease in the risk of mortality of 40% for patients who undergo surgery, with no indication of heterogeneity (HR=0.6 (0.45-0.78); I2=0). However we found indication for publication bias (P=0.03) suggesting that small studies published only mainly if they found significant results. Conclusions Our results suggest the benefit of surgical resection for advanced-stage melanoma. Patients with limited sites and numbers of metastases should be considered for curative resection regardless of the location of the disease.

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Predictive Factors for Additional Lymphatic Metastasis in Melanoma Patients with Positive Sentinel Node Biopsy E. Bertolli,* J.P. Duprat Neto, A.S. Molina, M.P. Macedo, C.A. Pinto, J.B. Bevilacqua. *Skin Cancer and Dermathology, Hospital AC Camargo, São Paulo, São Paulo, Brazil.*

Introduction: Sentinel node biopsy (SNB) is used to evaluate lymphatic disease and it can also provide prognostic information in melanoma patients. The identification of predictive factors for lymphatic metastasis after regional lymphadenectomy may have therapeutic impact. Objectives: To evaluate clinical and pathological correlation in patients with non sentinel node (NSN) involvement. Casuistic and methods: Retrospective study of the melanoma patients submitted to SNB in the Skin Cancer and Dermathology Department in the AC Camargo Hospital between the year 2000 to 2010. Results: In this period, 731 patients were submitted to SNB, which 144 (20%) had sentinel node disease. The medium number of identified and positive sentinel nodes were 2,3 and 1,2 per patient, respectively. It was performed 135 regional lymphadenectomies, 22 which (16%) had NSN positive. Micrometastasis were identified in 11% NSN negative patients and in 9% of the NSN positive patients (p=0,41). Conclusion: Involved margins in initial biopsy, sathelitosis in the primary tumor, elevated Breslow and mitotic index seen to be associated to aditional lymphatic involvement in melanoma patients with positive sentinel nodes.

	NSN Positive	NSN Negative	P
Margin			
Free	14/100 (14%)	86/100 (100%)	0,031*
Involved	6/17 (35%)	11/17(65%)	
Sathelitosis			
Negative	15/109 (14%)	94/109 (86%)	0,003*
Positive	5/10 (50%)	5/10 (50%)	
Mitotic index (per mm2)			
Median	9,2	3,7	0,028 **
Breslow (mm)			
Median	3,8	2,6	0,003**

* Pearson $\chi 2$ test; ** Wilcoxon test

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Management of Cutaneous Melanoma of the Nose J.S. Bond,* L. Haydu, M. Quinn, R. Saw, S. Jonathon, J.F. Thompson. *Surgical Oncology, Melanoma Institue Australia, Sydney, NSW, Australia.*

Cutaneous Melanoma of the nose is rare with little consensus regarding appropriate resection margins with poor understanding of lymphatic drainage pathways. A clinicopathologic review was undertaken of 182 patients with a diagnosis of primary cutaneous nasal melanoma treated in a single institution from 1969-2011. Statistical analyses utilized IBM SPSS Statistic 19.0. Median age at diagnosis was 70 years (males 59%) with a median Breslow thickness of 1.2mm (range 0.1-19mm). Median follow up was 31 months. The nasal tip (26%) and alar (21%) were most affected with superficial spreading melanoma (28%) the most frequent histologic tumor type. The median excision margin was 10mm (range 5-20mm). Full thickness skin grafting was used to reconstruct 58% of nasal tip and 34% of alar defects with a local flap employed in 9% and 27%. Overall 5 and 10 year disease-free survival was 56% and 39% respectively and was significantly influenced by increasing Breslow thickness (HR=1.27, 95% CI: 1.112-1.44, p<0.001), presence of ulceration (HR=3.21, 95%CI: 1.19-8.64, p=0.021) and wider excision margins (HR=0.076, 95%CI: 0.60-0.98, p=0.037) on multivariate analysis. Local recurrence occurred in 26 patients at a median time of 27 months (<1 to 84 months). Lymphoscintigraphy (LSG) was performed in 60 patients; 24 proceeded to SLNB of which 1 was positive. Regional recurrence occurred in 27 patients, 3 of whom had had SLNB performed (2 negative, 1 positive) and 7 had received preoperative LSG only. 10% of patients undergoing LSG displayed unexpected lymphatic drainage, with bilateral drainage observed in 23% of pastients with alar and sidewall melanomas. Overall 5 and 10 year melanoma-specific survival was 81% and 63% respectively and was significantly influenced by Breslow thickness (p<0.001), presence of ulceration (p<0.001), presence of dermal mitoses (p=0.019) and Clark level of invasion (p<0.001) on univariate analysis. Resection margins should not compromise local control given the reconstructive options. The unpredictability of lymphatic drainage from the skin of nose highlights the value of preoperative LSG, even if SLNB is not performed, by identifying sites of potential regional recurrence.

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Prognostic Significance of Lymphadenectomy in Esophageal Cancer Patients Receiving Neoadjuvant Chemoradiation C. Vijapura,[1]* R. Shridhar,[2] J. Weber,[2] S. Hoffe,[2] K. Alhamanna,[2] J. Deneve,[2] J. Barthel,[2] R. Karl,[2] K. Meredith.[2] *1. University of Missouri-Kansas City School of Medicine, Kansas City, MO; 2. Moffitt Cancer Center, Tampa, FL.*

Background: The optimal number of lymph nodes that should be harvested in esophageal cancer patients remains to be defined, particularly in patients that receive neoadjuvant therapies. We investigated the impact of nodal resection and survival in esophageal cancer patients treated with neoadjuvant chemoradiation (NT). Methods: Using our comprehensive esophageal cancer database we identified patients treated with NT followed by esophagectomy between 2000-2011. Clinical and pathologic data were compared using Fisher's exact and chi-square while, Kaplan Meier estimates were used for survival analysis. Overall (OS) and disease-free survival (DFS) were compared with varying numbers of lymph nodes resected <10 and ≥10 (ST-1), <12 and ≥12 (ST-2), and <15 and ≥15 (ST-3). Multivariate analysis was analyzed by the Cox proportional hazard model. Results: We identified 358 patients treated with NT and esophagectomy with a median follow-up of 18.5 months (range, 0-116 months). There was no survival benefit demonstrated for patients with increased lymph nodes removed during their surgery (ST-1 OS p=0.400, DFS p=0.8727; ST-2 OS p=0.6833, DFS p=0.6092; ST-3 OS p=0.1798, DFS p=0.4028). Patients were further stratified by pathologic response to NT and nodal harvest. There were no differences in OS or DFS in patients with increased nodal harvest when analyzed by complete (pCR) (ST-1 OS p=0.7278, DFS p=0.3602; ST-2 OS p=0.6182, DFS p=0.3592; ST-3 OS p=0.4489, DFS p=0.6976), partial (pPR) (ST-1 OS p=0.3762, DFS p=0.5061; ST-2 OS p=0.8036, DFS p=0.6497; ST-3 OS p=0.0890, DFS p=0.3364), or non response (pNR) (ST-1 OS p=0.6825, DFS p=0.7161; ST-2 OS p=0.7084, DFS p=0.8351; ST-3 OS p=0.5002, DFS p=0.7314) to NT. Multivariate analysis demonstrated that age (p=0.028), t-stage (p=0.006), pPR (p=0.025), and pNR (p<0.0005) to NT were all independent predictors of mortality. Conclusions: In our experience, the number of lymph nodes resected was not predictive for overall or disease free survival in esophageal cancer patients treated with NT. In addition, extended lymph node resection did not improve survival for those with residual disease.

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An Adaptable Acuity Care Unit (AACU) Model Facilitates Fast-tracking of Video-assisted Thoracic Surgery (VATS) Lobectomy Patients B. Nam,* T. Weigel. *University of Wisconsin, Madison, WI.*

Background With the current focus on health care cost reduction and outcomes, an Adaptable Acuity Care Unit (AACU) patient care model should facilitate fast-tracking the care of patients undergoing a thoracoscopic lobectomy. An AACU model allows for rapid transition between ICU, IMC, and general

levels of care without need for relocation of patients or change in nursing or physician providers. Our goal was to study the impact of this model on fast-tracking VATS lobectomy patients. Methods A retrospective review of prospectively collected data on one-hundred consecutive VATS lobectomies performed at the University from 1/2009 - 1/2011. All patients were admitted to the AACU post-operatively. To facilitate early discharge, we did not use epidural anesthesia. Instead, patients were begun on an oral long-acting opioid immediately pre-operatively. A patient-controlled anesthesia (PCA) pump was used post-operatively for one day and then the patient was transitioned to oral narcotics and NSAIDs. Chest tubes were placed to water seal immediately after surgery and then removed when the output was less than 300ml/day. Results Median age and FVC(%predicted) were 67 and 94%, respectively. Median LOS was 2 days with 94% of patients discharged to home. Immediate post-operative status was: general care in 69 patients, intermediate care in 30 patients and intensive care in 1 patient. Five (5%) patients developed atrial fibrillation requiring medical therapy. There were no instances of myocardial infarctions nor pneumonia and in-hospital and 30-day mortality were zero. Six patients (6%) were discharged with chest tubes for persistent air leaks. Seven (7%) patients were re-admitted within 30 days. Conclusions Patients who undergo a VATS lobectomy cared for in an AACU have short length of stays, few complications and a low re-admission rate. An AACU model facilitates fast-tracking of VATS lobectomy patients, enables most patients to be cared for as general care status, and decreases their length of stay(LOS); a surrogate endpoint of cost.

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99m-Tc-Tilmanocept in the Detection of Sentinel Lymph Nodes in Head and Neck Cutaneous and Intraoral Squamous Cell Carcinoma: Initial Experience S.Y. Lai,* M.D. Williams, B.A. Chasen, C.M. Lewis, A.C. Hessel, E.M. Rohren, J.N. Myers, R.S. Weber. *Head and Neck Surgery, MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: A prospective, multi-institutional, open-label, single arm trial has been initiated to assess the utility and accuracy of 99m-Tc-tilmanocept for the intraoperative identification of sentinel lymph nodes (SLN) in head and neck cutaneous and intraoral squamous cell carcinoma (HNSCC). We describe our initial experience with 99m-Tc-tilmanocept in SLN mapping in HNSCC patients. METHODS: Patients are enrolled with a diagnosis of primary oral cavity or cutaneous HNSCC (T1-T4a, N0, M0). The primary study endpoint is the false negative rate of 99m-Tc-tilmanocept indentified SLNs relative to the pathological status of non-SLNs in the elective neck dissection (END). Secondary measures of efficacy include diagnostic performance and rates of SLN detection. Patient safety is evaluated through observation and reporting of adverse events. RESULTS: Patient enrollment continues at 15 institutions, with a planned interim analysis at 50% accrual of patients with positive pathology. Our initial experience with 99m-Tc-tilmanocept in seven patients has shown the agent to be predictive of END pathology status. In the majority of our patients, we were able to inject the agent on the day prior to the surgical procedure, maintaining accurate preoperative imaging and a strong intraoperative signal, eliminating the complexity of timing surgery with same day injection and imaging. The ease of identification of SLNs (0-6 SLNs identified/pt, median 2) even prior to excision of the primary lesion, provided a better signal-to-noise ratio as compared to previous experience with 99m-Tc-labeled sulfur colloid. There have been no significant adverse events related to the use of 99m-Tc-tilmanocept. One serious adverse event was recorded (tongue bleeding), which resolved and was related to the surgical procedure at the primary site. CONCLUSIONS: 1. Injection of 99m-Tc-tilmanocept is feasible up to 30 hours prior to initiating surgical procedure 2. Clear delineation of primary lesion and candidate SLNs on SPECT-CT imaging 3. Concordance of SLN and END pathology findings 4. Improved signal-to-noise ratio during intraoperative localization

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Feasibility of Sentinel Node Biopsy in Head and Neck Melanoma using a Hybrid Radioactive and Fluorescent Tracer O.R. Brouwer,* M. Klop, T. Buckle, L. Vermeeren, M.W. Van den Brekel, A.F. Balm, O.E. Nieweg, R.A. Valdés Olmos, F.W. Van Leeuwen. *Nuclear Medicine / Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Noord Holland, Netherlands.*

Purpose: To examine the feasibility of combining lymphoscintigraphy and intraoperative sentinel node identification in patients with head and neck melanoma using a hybrid protein colloid that is both radioactive and fluorescent. Methods: A pilot study of eleven patients scheduled for sentinel node biopsy in the head and neck region was performed. Approximately five hours prior to surgery, the hybrid nanocolloid labeled with indocyanine green (ICG) and technetium-99m (99mTc) was injected intracutaneously in four deposits around the scar of the primary melanoma excision. Subsequent lymphoscintigraphy and single photon emission computed tomography with computed tomography (SPECT/CT) were performed to preoperatively identify the sentinel nodes. In the operating room, patent blue dye was injected in seven of the eleven patients. Intraoperatively, sentinel nodes were acoustically localized with a gamma ray detection probe and visualized using patent blue dye and/or fluorescence-based tracing with a dedicated near-infrared light camera. A portable gamma camera was used before and after sentinel node excision to confirm excision of all sentinel nodes. Results: A total of 27 sentinel nodes were preoperatively identified on the lymphoscintigrams and SPECT/CT images. All sentinel nodes could be localized intraoperatively. In the seven patients in whom blue dye was used, 43% of the sentinel nodes stained blue, while all were fluorescent. The portable gamma camera identified additional sentinel nodes in two patients. Ex vivo, all radioactive lymph nodes were fluorescent and vice versa indicating the stability of the hybrid tracer. Conclusions: ICG-99mTc-nanocolloid allows for preoperative sentinel node visualization and concomitant intraoperative probe and fluorescence guidance to the same sentinel nodes in head and neck melanoma patients.

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Day of Surgery Associated with Length of Hospital Stay in Patients Undergoing Lobectomy, Segmentectomy, and Wedge Resection C. Merkhofer,[1]* A. Kothari,[1] T. Bretl,[2] T.L. Weigel.[2] *1. University of Wisconsin School of Medicine and Public Health, Madison, WI; 2. University of Wisconsin Hospital and Clinics, Madison, WI.*

Introduction: Elucidation of factors contributing to prolonged length of hospital stay (LOS) can inform efforts to improve patient care and reduce healthcare costs. We hypothesized that the day of the week (i.e. Monday-Friday) of surgery does not impact median LOS. Methods: A total of 242 patients undergoing lobectomy or segmentectomy (n=161), wedge resection (n=57), or pneumonectomy (n=24) for a primary lung cancer at a major academic center between January 2009 and December 2010 were included in the study. Patient data was obtained from a prospectively collected and contemporaneously updated research database of all thoracic surgery patients at our institution. Multiple linear regression with ranks was used to determine whether day of surgery is associated with median LOS for the lobectomy/segmentectomy and wedge resection groups. Single linear regression with ranks was used for the pneumonectomy group. Results: Initial analysis showed that Friday lobectomy/segmentectomy patients had a longer median LOS (3.0 days, $p<0.015$) than the Monday reference (2.5 days). Multivariate analysis also showed a longer median LOS for Friday patients (2.7 days, $p<0.05$) than for their Monday counterparts (2.3 days). Tuesday, Wednesday and Thursday lobectomy/segmentectomy patients did not have a significantly different median LOS. Initial analysis showed no association between day of surgery and median LOS for wedge resection patients. Multivariate analysis showed that Friday wedge resection patients had a longer median LOS (3.7 days, $p=0.05$) than Monday patients (2.6 days). Wednesday and Thursday wedge resection patients did not have a significantly different median LOS. There was no association between day of surgery and median LOS among patients undergoing pneumonectomy. Conclusions: Our study suggests that patients undergoing lobectomy, segmentectomy or wedge resection on Friday are more likely to have a prolonged LOS than their counterparts undergoing surgery on Monday through Thursday. Further study is necessary to determine which factors contribute to greater LOS on Friday, and whether this association is present in a larger dataset.

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Intraoperative Frozen Section (FS) During Mediastinoscopy for Lung Cancer: Assessing Candidacy for Immediate Pulmonary Resection P. Perry,* M. Mount, B. Hird, R. Orr, C. Nguyen. *Spartanburg Regional Medical Center, Spartanburg, SC.*

INTRODUCTION Staging of mediastinal lymph nodes (MLN) by mediastinoscopy is of critical importance in assessing candidacy for lung resection. Often, mediastinoscopy is performed as a sole procedure, with permanent pathology results guiding subsequent surgical intervention. Our practice

has been to perform mediastinoscopy followed by immediate surgical resection, as indicated, based on intraoperative FS assessment of MLN. The goal of our study is to evaluate the accuracy of FS analysis when compared to permanent sections (PS), and identify factors that may lead to discordance. METHODS A retrospective review of patients with lung cancer that underwent mediastinoscopy from June 2006 to January 2011. All patients received clinical staging according to NCCN guidelines and were considered potential candidates for surgical resection. FS and PS results of MLN were compared. RESULTS Mediastinoscopy was performed on 191 patients, with a total of 549 MLN (spanning levels 2R, 2L, 4R, 4L, 7, 10R) assessed by both FS and PS. On final pathology, 67 patients (35.1%) had at least 1 positive MLN, while 124 patients (64.9%) had all negative MLN. Concordance between FS and PS was found in 545 MLN (99.3%). All 4 discordant MLN were initially read as negative on FS and involved 4 different patients. One case involved a patient who underwent mediastinoscopy after neoadjuvant chemoradiation. In the remaining 3 cases, additional MLN were identified to be positive by FS at the time of mediastinoscopy. Overall accuracy of FS analysis for detecting malignancy was 97.9%, with a sensitivity of 94.3% and specificity of 100%. Positive predicted value was 100% and negative predicted value was 96.7%. CONCLUSION Our data suggest that for lung cancer patients with potentially resectable tumors, immediate FS analysis of MLN followed by definitive surgery is a reliable and safe strategy. Discordance with final pathology was rare (0.7% of MLN) and resulted in improper staging of only 1 patient (0.5%). Advantages of this approach include less medical costs (single operating room/anesthetic charge) and hastening of time from diagnosis/staging to definitive treatment.

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Is Robotic-assisted Thoracoscopic Lobectomy (RATL) Better than Video-assisted Thoracoscopic Lobectomy (VATL)? B. Dalton,* D.D. Barrineau, R.B. Hird, R.K. Orr, C.L. Nguyen. *Spartanburg Regional Medical Center, Spartanburg, SC.*

Introduction: Over the last several years, VATL has been our preferred approach for early stage non-small cell lung cancer (NSCLC). Recently, we have adopted robotic technology for such patients. The purpose of our study is to investigate the safety of RATL and to compare our early robotic experience with our historical VATL outcomes. Methods: We reviewed our first 20 RATL patients (October 2010 to August 2011) and compared them to our most recent 37 VATL patients (January 2009 to September 2010). All patients underwent standard pre-operative staging and received standard mediastinal lymphadenectomy at the time of the resection. Data regarding patient characteristics, length of stay (LOS), chest tube (CT) days, pathologic staging, postoperative complications, estimated blood loss (EBL), operative time and 30-day mortality were analyzed. Results: Patient characteristics were similar among the two groups. RATL was successfully completed in 16 of 20 patients (80%) with 3 patients converted to thoracotomy and one to VATL. No patients in the VATL group required conversion. There was no difference in operative time (322 +/- 65min for RATL vs. 245 +/- 69min for VATL, p=ns) or EBL (203 +/- 381 mL for RATL vs. 172 +/- 154 mL for VATL, p=ns). When the indication for resection was NSCLC the majority of both populations were stage I (67 % for RATL and 70 % for VATL). Average lymph node (LN) yield with RATL was 13.1 +/- 8.0 compared to 7.7 +/- 3.9 with VATL (p=0.006). Complication rate was 25% for RATL and 30% in VATL population. Thirty-day mortality for both groups was 0. Post-operative CT duration for RATL was 3.2 +/- 0.9 days compared to 4.1 +/- 3 days for the VATL group (p=0.03) and LOS for RATL was 5.0 +/- 2.1 days compared to 6.7 +/- 3.4 days for the VATL group (p=0.01). Conclusion: The use of RATL for early stage NSCLC appears safe and feasible. Comparison of our early RATL data with our established VATL data suggests advantages of improved LN yield, shorter CT days and shorter LOS with RATL. Although our experience with RATL is early, these provocative data have significant implications for improving tumor LN staging and patient recovery.

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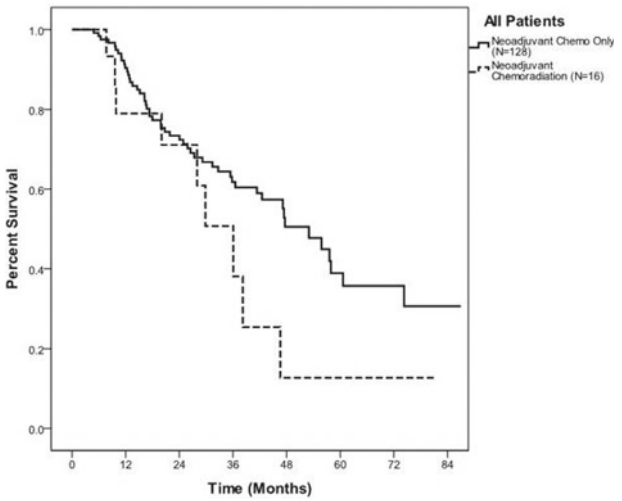
Preoperative Radiation Therapy in the Treatment of Resectable Esophageal Adenocarcinoma: Is There Really a Benefit? B. Allan,* F. Pedroso, A.T. Prescott, A. Montero, B. Lally, B. Ardalan, A.S. Livingstone, L.G. Koniaris, D. Franceschi, N.L. Solomon. *University of Miami, Miami, FL.*

Introduction: The role of adjuvant or neoadjuvant radiation therapy in treatment of esophageal adenocarcinoma (EAC) remains controversial. Our aim was to determine if neoadjuvant radiotherapy as an added strategy for the treatment of resectable esophageal adenocarcinoma portends a survival benefit. Methods: A retrospective examination of a prospectively collected data set of resectable adenocarcinomas of the esophagus and gastro-esophageal junction. Results: A total of 198 patients with EAC were treated between 2000 and 2008. Overall 30 day, 1 year and 5 year survival was 97%, 88% and 44% respectively. 128 pts (64.7%) received neoadjuvant chemotherapy, 16 pts (8.1%) received neoadjuvant chemoradiation, and 54 pts (27%) had surgery only. Five year survival for patients receiving neoadjuvant chemotherapy and neoadjuvant chemoradiation were 40% and 13% respectively (p=0.112). Of the patients receiving neoadjuvant chemotherapy, 52 (40.6%) were downstaged, 15 (11.7%) had a complete pathological response, and 47 (36.7%) had no change or progressive disease. Patients receiving neoadjuvant chemotherapy who were downstaged had significantly greater five year survival than those with no response or progressive disease, 64% vs. 15% (p<0.0001). Conclusions: Peri-operative and long-term outcomes for patients with adenocarcinoma of the esophagus continue to improve versus historical controls; however the most beneficial treatment approach remains in question. Our data suggests neoadjuvant chemotherapy alone to be associated with an improved five-year survival as compared to neoadjuvant chemoradiotherapy in patients with resectable EAC. Additionally, good response to neoadjuvant chemotherapy confers a survival benefit.



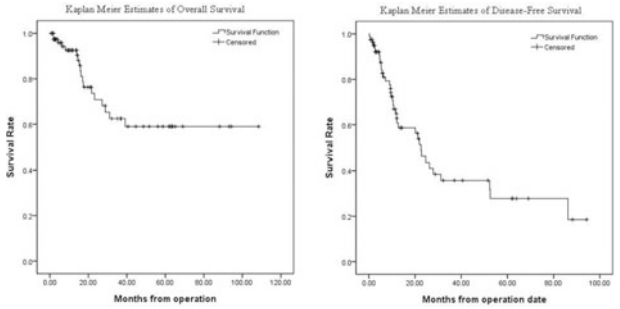
Percent Survival with Neoadjuvant Chemotherapy versus Neoadjuvant Chemoradiotherapy

P304

Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Asian Patients: A 10-year Experience in a Single Institution G. Tan,* M. Teo, W. Chan, K. Soo. *National cancer centre singapore, Singapore, Singapore.*

Background: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been shown to improve survival in selected patients with peritoneal carcinomatosis. We review our institutional 10-year experience with the procedure and evaluate the overall and disease-free survival rates in our Asian patients. Method: Data was prospectively collected from all patients with peritoneal carcinomatosis treated by CRS and HIPEC at the National Cancer Centre Singapore between April 2001 and June 2011. Our primary end points were overall and disease-free survival. Results: A total of 81 patients underwent CRS and HIPEC. Of the 81 patients, 68 (84%) were of Chinese ethnicity, 3.7% were Malay, 3.7% were Indian and 8.6% were of other ethnicities. Primary tumours were ovarian cancer (n=32), colorectal cancer (n=23), primary peritoneal (n=5), appendiceal cancer (n=13), Mesothelioma (n=6), gastric cancer (n=1) and endometrial cancer (n=1). At 3 years, the disease-free survival was 35.7% and overall survival was 62%. Factors influencing overall and disease-free

survival were tumour type, operation time, PCI score >15, intraoperative blood loss,post operative transfusion,time to starting feeds, requirement for bilateral chest tubes and the number of days in the intensive care unit on univariate analysis. The only factors that remained significant for prognosis after multivariate analysis were PCI score >15 and the need for bilateral chest tubes. Chest tubes were inserted when stripping of the diaphragmatic peritoneum was required. Conclusion: CRS and HIPEC is an aggressive procedure that confers significant disease-free and overall survival to Asian patients with peritoneal carcinomatosis .



Factors associated with Overall Survival

VARIABLE	10 year OS (%)	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Gender Male Female	33.5 39.9	21.7 - 45.2 30.1 - 49.7	0.08	0.766	0.53 - 1.09	0.143
Age* < 46 ≥46	38.4 35.9	27.6. - 49.1 24.2 - 47.6	0.591			
Disease Free Interval ≤6 months > 6 months	32.1 41.7	20.4 - 43.8 31.9 - 51.	0.026	0.692	0.48 - 0.99	0.046
Extent of disease Unilateral Bilateral	39.0 30.6	31.1 - 46.8 14.9 - 46.2	0.99			
Resection Complete Incomplete	38.4 21.1	29.8 - 47.0 0.0 - 52.5	0.123			
Extent of resection Wedge Major**	38.5 26.7	28.7 - 48.3 11.2 - 42.1	0.036	1.48	1.01 - 2.2	0.043
Approach Staged Bilateral	38.9 19.3	30.4 - 47.3 0 - 41.1	0.22			
Number of metastases Single Multiple	39.5 34.9	27.7 - 51.2 25.1 - 44.7	0.892			
Size <3 cm ≥3cm	43.0 31.4	33.2 - 52.8 18.2 - 44.5	0.464			

* Median age for all patients excluding germ-cell tumors. ** Major resections includes anatomic segmentectomy, lobectomy and pneumonectomy

P305

An 18-year Cohort of Patients Treated with Lung Metastasectomy: A Single-center experience J.F. Corona-Cruz,[1]* L.M. Dominguez-Parra,[1] D. Saavedra-Perez,[3] E. Jimenez-Fuentes,[1] L. Green-Schneweiss,[1] M. Rios-Trejo,[3] D. Pachuca,[3] E. Guzman-de Alba,[1] A. Padilla-Rosciano,[1] H. Martinez-Said,[1] O.G. Arrieta-Rodriguez.[2] *1. Surgical Oncology Instituto Nacional de Cancerologia, Mexico City, Mexico; 2. Medical Oncology Instituto Nacional de Cancerologia, Mexico City, Mexico; 3. Laboratory of Experimental Oncology Instituto Nacional de Cancerologia, Mexico City, Mexico.*

Introduction: Resection of lung metastases has been an area of controversy in oncology. There are not controlled trials and most of the evidence comes from small cohorts with a short follow-up. The aim of this study is to report our experience with lung metastasectomy for several malignancies. Methods: We retrospectively reviewed patients who underwent lung metastasectomy from January 1990 to December 2008. Variables related to the tumor and surgical procedure were included. Univariate and multivariate analysis was performed to identifiy factors associated with overall survival (OS) Results: We included 398 patients. Mean follow-up was 20 months. There were 237 men. Median age was 35 years. Primary tumor were germ-cell in 126 cases, soft-tissue sarcomas in 87, breast cancer in 40 and renal-cell carcinoma in 35. A disease free interval (DFI) >6 months was identified in 303. Single metastases was present in 157 cases and 241 have multiple. Wedge resection was performed in 297, and a major procedure in the rest. One metastasectomy was performed in 285 cases, up to five re-do metastasectomy were done. A complete resection was achieved in 351 patients (88.2%) Median OS for all patients was 81.9 months. Ten-year OS for Germ-cell tumors was 62.2% and 37.1% for all non-germ cell tumors. Ten-year OS for cervical cancer was 56.5%, osteosarcoma 46.0%, colo-rectal cancer 44.4%, head and neck tumors 39.4%, breast cancer 38.3%, soft-tissue sarcomas 28.2% and renal-cell carcinoma 21.4%. In multivariate analysis factors associated with OS were DFI >6 months (HR 0.692, CI 95% [0.48 – 0.99] p = 0.046) and major resection (1.48 [1.01 – 2.2] p = 0.043) Patients with a complete resection showed a better OS compared with those with residual disease, but it was not statistical significant (38.4 vs 21.1 p = 0.123) Conclusions: Lung metastasectomy may achieve long-term survival in well-selected patients. Factors associated with a better OS were a DFI >6 months and requiring only a wedge resection. Although not significant, a complete resection showed a trend to better OS and is strongly advisable. Size and number of metastases as well as re-do surgery are not associated with worst survival

P306

Establishing a HIPEC Program: What is the Financial Impact? C.X. Cruz Pico,* P. Escobar, S. Chalikonda, M. Walsh, G. Falk, C. Michener, A. Thompson. *Cleveland Clinic Foundation, Cleveland, OH.*

Cytoreductive Surgery (CRS) and Hyperthermic Chemotherapy (HIPEC) are considered a therapeutic modality to treat selected patients with peritoneal carcinomatosis arising from several primary cancers. These treatments have been implemented successfully in tertiary care centers with high number of cancer referrals. We present our experience with the first 39 patients who underwent CRS and HIPEC for intraperitoneal malignancies at our institution, and analyze the financial implications involved in starting a new HIPEC treatment program. Data was collected by a retrospective review of a prospectively maintained database of patients undergoing CRS and HIPEC since the establishment of the program in 4/2009 to 12/2010. Data collected included: demographics, net revenue generated, and costs accrued. Technical cost was broken down by the resource utilization areas of anesthesia, imaging, nursing, pathology, pharmacy, surgical services, and hospital stay (ICU and non-ICU). The contribution margin and net income for this service was also calculated. A total of 39 patients underwent CRS and HIPEC from 4/2009 to 12/2010. Male to female ratio was 1:3, Median age 53.2 years (range 28-76) years. The malignancies treated were primary peritoneal mesothelioma (n=4), gastric (3), ovarian (7), appendiceal (9), pseudomyxoma peritonei (8), colonic (8), cervical (1), gallbladder (1), urothelial (1) and duodenal (1). The median Peritoneal Cancer Index (PCI) was 9.4 (range 0 to 39). R0 resection was achieved in 32 patients. The total revenue generated was $4,025,967 with a contribution margin of $2,631,940 (revenue – direct costs). Total costs were $2,289,069 yielding a net income of $1,736,897 or an average of $44,535.83 per patient. The majority of costs were attributable to surgical services (40.6%), nursing (27.44%), pathology and laboratory (10.42%), and pharmacy (9.21%). We provide an initial estimate of the costs involved in implementing and running a successful CRS and HIPEC program in an academic center. Although the procedures are generally complex, and utilize extensive resources; providing this state of the art therapy can be achieved without financial loss to the hospital.

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Correlation of Liquid Density and Malignant Diagnosis in Cystic Ovary Tumors F.T. Lissa,* R. Amante, M. Rosa. *Surgical Oncology, Hospital São José, Criciuma, Santa Catarina, Brazil.*

Tumors of the ovary ranks fourth in frequency of causes of gynecological surgery. The differentiation between benign and malignant is crucial for an optimal treatment, but the accuracy of clinical, laboratory and imaging is poor, leading to a high false-positive results. To know the correlation of the liquid density of ovarian cystic tumors on CT, we colected data of 30 pacients undergoing surgical treatment. We did a cross sectional, retrospective study that evaluated the outcome of the density of ovarian tumor imaging with CT compared to pathological results in all pacients in our institution from 2008 to 2010. We analyzed 30 cases. Of these, 16 cases 40%) were diagnosed with malignant tumor, 18 (60%) cases were benign tumors, was regarded as evil, then adding to 75%. Among the benign tumors, the densities ranged from 5 to 24 UH (only one patient had density over 20), with a average of 12.5 UH. Malignant tumors had densities ranged from 24 to 42, with a average of 28. The average age of the benign tumors was 42.6 years, and in malignant tumors was 53,3 years. There was no positive correlation between densities and the size, stage and age of the patients. The densities observed in cystic tumors of ovary by computed tomography contributed to the differential diagnosis between benign and malignant tumors, using a baseline of 20 UH or more for the diagnosis of malignant tumors. This relationship could serve as a tool for a differential diagnosis of ovary cystic tumors.

Patients and diagnosis

	Benign	Malignant
Age (median)	42,6	53,3
Density (UH)	12,5	28

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Malignancies among Kidney Transplant Recipients: A 5-year Analysis of 85,307 Kidney Transplant Recipients from the Nationwide Inpatient Sample Database C. Dragon,* S. Patil, R. Chamberlain. *Surgery, Saint Barnabas Medical Center, Livingston, NJ.*

Introduction Cancer following kidney transplantation (KT) is a source of significant mortality and morbidity. It is the third most common cause of death in this population. Most cancers develop *de novo*, however some may represent progression or recurrence of preexisting lesions in either the recipient or within the donor organ. We analyzed the incidence and gender and ethnic variations in *de novo* malignancies in KT recipients. Materials and Methods Discharge data involving 85,307 KT patients between 2004 and 2008 from the Nationwide Inpatient Sample (NIS) database a part of the Healthcare Cost and Utilization Project (HCUP) was abstracted. Age, gender, race and type of malignancy were studied. Patients were grouped according to those who developed a malignancy and those who did not. Categorical variables were compared using the Chi square test and the Student's t test was used to compare continuous variables. Results A total of 8314 malignancies were identified in 5959 (7%) KT patients. The mean age of KT patients with malignancy was 58.0 years compared to 50.9 years in those without malignancy, $p < 0.001$. Gender information was available for 99.9% (N=85268) of patients and ethnicity was available for 75.7% (N = 64,553). 7.8% (N=3628) of male KT patients and 6.0% (N=2320) of female KT patients developed a *de novo* malignancy, $p < 0.001$. Hematological cancer was most common in males (N = 797, 1.7%) compared to breast cancer (N = 600, 1.6%) in females. The most common malignancy in Caucasians was non-epithelial skin cancer (N = 851, 2.19%), urinary tract cancer in African Americans (N = 165, 1.31%), hematological cancer in Hispanics (N = 119, 1.34%), and gastrointestinal cancer in both Asians/Pacific Islanders (N = 38, 1.85 %) and Native Americans (N= 12, 1.88%, Table 1). Conclusions KT recipients are at a high risk of developing *de novo* malignancies. Age >58 years, Caucasian ethnicity (71.1%) and male sex (61%) are additional risk factors. Hematological malignancies are the most common primary malignancies (1.47%) followed by non-epithelial skin cancer (1.38%) and urinary tract malignancies (1.2%).

Table 1. Distribution of cancer subtypes that occurred subsequent to kidney transplantation among 85,307 kidney transplant recipients from National Inpatient Sample database between 2004 and 2008 grouped according to gender and race of patients

Cancer subtypes	Distribution of cancer subtypes based on Gender			Distribution of cancer subtypes based on Race						
	Overall, N= 5948	Males, N= 3628 (7.8%)	Females, N= 2320 (6.0%)	Overall, N= 6529	Caucasians, N=4607 (70.5%)	African Americans, N= 916 (14%)	Hispanics, N=618 (9.5%)	Asians or Pacific Islanders, N=196 (3%)	Native Americans, N= 45 (0.6%)	Others, N= 147 (2.2%)
Hematological cancer, N= (%)	1252 (1.47)	797 (1.70)	455 (1.18)	936 (1.45)	672 (1.73)	79 (0.63)	119 (1.34)	34 (1.65)	7 (1.10)	25 (1.59)
Non-Epithelial skin cancer, N= (%)	1177 (1.38)	785 (1.68)	392 (1.02)	927 (1.44)	851 (2.19)	13 (0.10)	30 (0.34)	11 (0.54)	3 (0.47)	19 (1.20)
Urinary tract cancer, N= (%)	1024 (1.20)	717 (1.53)	307 (0.80)	801 (1.24)	511 (1.32)	165 (1.31)	75 (0.84)	33 (1.61)	3 (0.47)	14 (0.89)
GIT cancer, N= (%)	834 (0.98)	522 (1.12)	312 (0.81)	647 (1.00)	416 (1.07)	97 (0.77)	74 (0.83)	38 (1.85)	12 (1.88)	10 (0.63)
Malignant neoplasms NOS, N= (%)	714 (0.84)	458 (0.98)	256 (0.66)	516 (0.80)	333 (0.86)	60 (0.48)	64 (0.72)	19 (0.92)	8 (1.26)	32 (2.03)
Male genital tract cancer, N= (%)	628 (0.74)	628 (1.34)		501 (0.78)	305 (0.79)	136 (1.08)	35 (0.39)	9 (0.44)	4 (0.63)	12 (0.76)
Lung cancer, N= (%)	603 (0.71)	417 (0.89)	186 (0.48)	465 (0.72)	356 (0.92)	64 (0.51)	24 (0.27)	8 (0.39)	1 (0.16)	12 (0.76)
Breast cancer, N= (%)	605 (0.71)	5 (0.01)	600 (1.56)	482 (0.75)	330 (0.85)	92 (0.73)	32 (0.36)	15 (0.73)	1 (0.16)	12 (0.76)
Female genital tract cancer, N= (%)	392 (0.46)		392 (1.02)	420 (0.65)	200 (0.52)	132 (1.05)	74 (0.83)	8 (0.39)	0 (0.00)	6 (0.38)
Other Primary cancers, N= (%)	376 (0.44)	207 (0.44)	169 (0.44)	278 (0.43)	205 (0.53)	20 (0.16)	39 (0.44)	7 (0.34)	2 (0.31)	5 (0.32)
Head and Neck cancer, N= (%)	324 (0.38)	247 (0.53)	77 (0.20)	250 (0.39)	191 (0.49)	33 (0.26)	22 (0.25)	1 (0.05)	2 (0.31)	1 (0.06)
Melanoma, N= (%)	195 (0.23)	133 (0.28)	62 (0.16)	160 (0.25)	147 (0.38)	6 (0.05)	2 (0.02)	2 (0.10)	0 (0.00)	3 (0.19)
HPB cancer, N= (%)	190 (0.22)	144 (0.31)	46 (0.12)	153 (0.24)	90 (0.23)	19 (0.15)	28 (0.31)	11 (0.54)	2 (0.31)	3 (0.19)

Abbreviations: N, number of patients; GIT, gastrointestinal tract; NOS, not otherwise specified; HPB, hepatobiliary and pancreatic

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Outcomes for Patients who are Diagnosed with Both Breast and Endometrial Cancer T. Martin-Dunlap,[1] M.S. Wachtel,[2] J.A. Margenthaler.[1]* *1. Department of Surgery, Washington University School of Medicine, St. Louis, MO; 2. Texas Tech University Health Sciences Center, Lubbock, TX.*

Introduction: Of all new cancers diagnosed in women each year, approximately 30% are attributed to breast cancer and 6% to endometrial cancer. As the population ages and treatment modalities become more effective, it will become more common to diagnose both cancers during a single patient's lifetime. The overall survival outcomes for patients who are diagnosed with both cancers have not been previously reported. Methods: Using the 1988-2007 Surveillance, Epidemiology, and End Results data, we conducted a retrospective, population-based cohort study of women diagnosed with both breast and endometrial cancer. Kaplan-Meier survival curves were created for disease-specific survival. Wald chi square tests evaluated differences between survival estimates. Results: We identified 2,027 women who were diagnosed with both breast and endometrial cancer. Of these, 1,296 (63.9%) were diagnosed with breast cancer first and 731 (36.1%) were diagnosed with endometrial cancer first. The median age at the second cancer diagnosis was 68 years (range 60-76), and the median time between the first cancer diagnosis and the second cancer diagnosis was 45 months (range 17-81). Regional lymph node involvement was significantly more common with a breast cancer diagnosis [522 (25.8%) women] compared to an endometrial cancer diagnosis [87(4.3%) women] ($p<0.05$). Factors associated with decreased survival included high tumor grade, nodal positivity, and estrogen receptor-negative breast cancer ($p<0.05$ for each). At the end of the study, 1,703 (84%) patients were still living. There were 83 (4.1%) deaths due to breast cancer, 63 (3.1%) deaths due to endometrial cancer, and 178 (8.8%) deaths due to other causes ($p<0.05$). Discussion: For women diagnosed with both breast and endometrial cancer, the cumulative risk of death at 5 years following the second cancer diagnosis

is nearly four times more likely to be due to breast cancer than endometrial cancer. Breast cancer-specific mortality increases with time, while endometrial cancer-specific mortality decreases with time. Consideration should be given to these findings when discussing prognosis and making treatment decisions.

P310

Single Incision Laparoscopic Splenectomy: Preliminary Experience in Consecutive Patients and Comparison to Standard Laparoscopic Splenectomy B.A. Boone,* P. Wagner, E. Ganchuk, L. Evans, H.J. Zeh, D.L. Bartlett, M.P. Holtzman. *Surgery, University of Pittsburgh, Pittsburgh, PA.*

Introduction Since first being described in 2009, single incision laparoscopic splenectomy has been described in a limited number of case reports and small case series. No studies have evaluated single incision splenectomy in unselected patients and outcomes of the procedure have not previously been compared to standard laparoscopy. Methods A retrospective review was conducted to evaluate all single incision splenectomies performed by a single surgeon between June 2010 and June 2011. Additionally, patients who underwent standard laparoscopic splenectomy by five surgeons in the same tertiary referral surgical oncology group from June 2008 to June 2011 were evaluated to serve as a control group. Demographic data, operative parameters and post-operative outcomes were assessed. Results Eight patients underwent successful single incision splenectomy during the study period without conversion to open or requiring additional ports. The median operative time was 92.5 minutes. There was no mortality and 25% morbidity in the study group. Median length of stay was 4 days. Additionally, eighteen patients who underwent standard laparoscopic splenectomy were evaluated for comparison. No significant differences were identified in the preoperative patient characteristics between the two groups. Single incision splenectomy was associated with a statistically significant shorter operative time (92.5 min vs. 172 min, p=0.003), a lower conversion rate, comparable blood loss, equivalent length of stay, reduced mortality, similar morbidity and comparable postoperative narcotic requirements. Conclusions Single incision splenectomy is feasible, safe and efficient in an unselected patient population in the hands of an experience laparoscopic surgeon. The single incision technique is comparable to standard laparoscopic splenectomy in terms of operative time, peri-operative outcomes. Further study is warranted.

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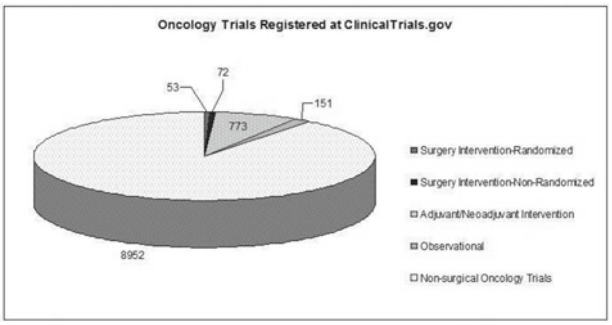
Clinical Research in Surgical Oncology: An Analysis of ClinicalTrials.gov A.S. Menezes,* A. Barnes, A.S. Scheer, H. Moloo, R. Boushey, R. Auer. *General Surgery, University of Ottawa, Ottawa, ON, Canada.*

INTRODUCTION The conduction of randomized clinical trials has expanded in medical specialties, but to a far lesser degree in surgery. This is due to design challenges with standardization of treatment, blinding and lack of surgeon equipoise. The objective of this study was to assess the current landscape of clinical trials in surgical oncology registered at clinicaltrials.gov. METHODS Data was extracted from clinicaltrials.gov using the following search engine criteria: 'Cancer' as Condition, 'Surgery OR Operation OR Resection' as Intervention, and Non-Industry sponsored. The search was limited to Canada and the United States and included trials registered from January 1, 2001 to January 1, 2011. The search was performed on March 23, 2011 by three investigators in parallel. The total number of oncology trials was also obtained. RESULTS Of 9990 oncology trials, 1049 (10.5%) included any type of surgical intervention. Of these trials, 125 (11.9%; 1.3% of all oncology trials) manipulated a surgical variable, 773 (73.7%) assessed adjuvant/neoadjuvant therapies, and 151 (14.4%) were observational studies. Trials assessing adjuvant therapies focused on systemic treatment (362 trials, 46.8%) and multimodal therapy (129 trials, 16.7%). Of the 125 trials where surgery was the manipulated variable, 59 trials (47.2%) focused on surgical techniques (including minimally invasive) or devices, 45 trials (36.0%) studied invasive diagnostic methods, and 21 trials (16.8%) evaluated surgery vs. no surgery. The majority of the 125 trials were non- randomized (72, 57.6%), and Phase III trials accounted for less than one-quarter (29, 23.2%). CONCLUSIONS The number of registered surgical oncology trials is small in comparison to oncology trials as a whole. Clinical trials specifically designed to assess surgical interventions are vastly outnumbered by trials focusing on adjuvant therapies, and are frequently non-randomized. Randomized surgical oncology trials account for <1% of all registered cancer trials. Barriers to the design and implementation of randomized trials in surgical oncology need to be clarified in order to facilitate higher-level evidence in surgical decision making.



P312

Socioeconomic and Geographic Disparities in Immediate Reconstruction after Mastectomy in the United States B.A. Wexelman,[1]* X. Ma,[2] D. Boone,[1] S. Rosenbaum Smith,[1] P.I. Tartter,[1] A. Estabrook,[1] A.T. Ma.[1] *1. Department of Surgery, St Luke's-Roosevelt Hospital Center, New York, NY; 2. Department of Statistics, Columbia University, New York, NY.*

Introduction: Disparities are found in breast cancer diagnosis, treatment, and outcomes. We seek to determine if socioeconomic and geographic disparities exist nationally in immediate reconstruction type after mastectomy. Methods: This retrospective study compares socioeconomic and geographic features for 14,986 women who underwent mastectomy in 2008 using the Nationwide Inpatient Sample (NIS), an all-payer stratified statistical sample of all US hospital discharges. Statistical analysis was performed to understand variations between three groups: patients without reconstruction (NR), patients who underwent breast implant/ tissue expander reconstruction (TE), and patients with advanced reconstruction techniques such as free or pedicled flaps (FLAP). Results: The majority of women (63%) had no reconstruction (NR), while 25.3% had TE and 12% underwent FLAP. Compared to patients with NR, women with TE or FLAP were younger (64.9 years vs. 51.3 & 51.1 years, p<0.001), had fewer chronic conditions (3.85 NR vs. 2.60 TE & 2.54 FLAP conditions, p<0.001), and higher mean hospital charges ($22,300 NR vs. $42,850 TE and $48.680 FLAP, p<0.001). The length of stay was longest for FLAP patients (3.62 days) compared to the NR group (2.02 days) and the TE group (1.90 days), p<0.001. Caucasians were disproportionately more likely to undergo both TE and FLAP compared to Black and Hispanic women. Patients with FLAP reconstruction were more likely to have private insurance (81.1%), than TE (80.1%) and NR (35.2%) while women without reconstruction were more likely to have Medicare and Medicaid insurance. Compared to NR, those undergoing reconstructions were more likely to live in zip codes with higher average incomes and more likely to live in or near a major city (>1 million people). Conclusions: This is the first national study analyzing patients of all insurance types and regions of the US to show statistically significant disparities in the type of immediate reconstruction after mastectomy based on age, race, insurance type, and geographic location.

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An Evidence-Based Proposal of Oncology-Specific Risk Factors for Morbidity and Mortality after Complex Cancer Surgery T.A. Aloia,[1]* A.B. Cooper,[1] V.E. Strong,[2] W.J. Hoskins,[2] M. Sovel,[2] W. Shi,[1] V.S. Jordan,[1] G.J. Chang,[1] J.M. Skibber,[1] J.E. Lee,[1] P.T. Pisters.[1] *1. Surgical Oncology, MD Anderson, Houston, TX; 2. Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Early postoperative morbidity and mortality can significantly impact long-term cancer survival. The American College of Surgeons-National Surgical Quality Improvement Program (NSQIP) actively collects data on perioperative risk and outcomes associated with multiple general surgery operations, but only recently has developed an Oncology Consortium to focus on patients with malignancy undergoing complex cancer surgery. One of the stated goals of the Consortium is to determine the relative contribution of cancer-specific risk factors to early postoperative outcomes. The purpose

of this project was to identify a set of perioperative cancer-specific risk factors that could be prospectively investigated for their ability to predict 30-day postoperative morbidity and mortality relative to traditional NSQIP general surgical risk factors (e.g. ASA score, albumin, functional status). **Methods:** Using literature review and applying RAND methodology to expert panel input, multiple potential candidate cancer-specific variables were subjected to the following inclusion/exclusion criteria: previously documented association with 30-day outcomes, ability to be captured by a surgical clinical reviewer (SCR) from available clinical documentation, and not currently a NSQIP data variable. **Results:** Of 22 candidate variables assessed (Table), the following perioperative risk factors satisfied all inclusion criteria: 1) surgery for recurrent malignancy, 2) cancer-related pain requiring narcotic therapy within 30 days of surgery, 3) oncologic intent of surgery (curative versus palliative), and 4) extent of resection relative to T and N stage (standard versus extended resection). **Conclusions:** Using a comprehensive methodology, several potential cancer-specific risk factors for short-term outcomes in complex cancer surgery were identified. These variables can be prospectively validated and subsequently considered for inclusion in data collection and risk modeling within the group of National Cancer Institute-designated cancer centers participating in the ACS-NSQIP-Oncology Consortium.

Candidate Risk Factor	Associated with 30-day Outcomes	Not Included in NSQIP	Consistently SCR Accessible
Preoperative Variables			
1. Functional Status	x		
2. Chemotherapy within 30 days	x		x
3. Radiation therapy within 90 days	x		x
4. Cancer pain requiring preoperative narcotics	x	x	x
5. Steroid therapy	x		x
6. Weight loss >10% within 6 months	x		
7. Metastatic cancer	x		x
8. Anemia	x		x
9. Thrombocytopenia	x		x
10. Leukopenia	x		x
11. Transfusions	x		x
Perioperative Variables			
1. Anesthetic: general, general + regional, regional, IV	x		x
2. Surgical intent: benign, malignant curative, malignant palliative	x	x	x
3. Multiteam procedure		x	x
4. Staged procedure		x	x
5. Routine vs. extended resection based on T and N stage	x	x	x
6. Reoperative field	x	x	
7. Surgery for recurrent malignancy	x	x	x
Postoperative Variables-General			
1. Initial primary postoperative analgesia: epidural, regional, IV opiates, oral opiates, non-opiates		x	x
Postoperative Variables-Pathology			
1. Histology		x	x
2. TNM stage		x	x
3. Resection status (R0,R1, R2)		x	x

P314

Implementation of a Multidisciplinary Thyroid Center Improves Precision and Diagnostic Efficiency in Patients Requiring Thyroid Surgery S. Tohme,* K.L. McCoy, L. Yip, S.P. Hodak, M.T. Stang, C. Coyne, S.O. LeBeau, S.E. Carty. *University of Pittsburgh, Pittsburgh, PA.*

Introduction: Although a multidisciplinary approach to patient care is reported to have several advantages, its utility remains controversial. Thyroid nodule evaluation and management relies on multidisciplinary expertise. We evaluated comparative care efficiencies for thyroid nodule patients after implementation of a Multidisciplinary Thyroid Center (MTC). Methods: Initiated in 9/08, a physician-organized MTC staffed by thyroid disease specialists including surgeons, endocrinologists, radiologists and cytopathology technicians was designed to facilitate same day testing when indicated and triage patients to be seen by the appropriate physician. The evaluation parameters of new surgical MTC patients seen by 1 surgeon were compared to those of a traditional single-specialty clinic (non-MTC) during the same time period. The degree of necessary clinical evaluation was compared according to the 2009 American Thyroid Association (ATA) Guidelines. Results: During the study period 428 new patients were seen for a thyroid nodule by 1 endocrine surgeon (139 MTC patients v 289 non-MTC). As predicted by selection criteria, new MTC patients were more likely to have an indication for thyroid surgery by the ATA Guidelines (79% v 62%, p<0.001), were more likely to schedule surgery at the initial visit (79% v 63%, p=.01) and had a shorter mean time from initial consultation to thyroidectomy (27 v 33 days, p=0.03). In addition, MTC patients required fewer preoperative physician visits (mean 1.6 v 2.1, p<.001) and thyroid cancer patients evaluated in the MTC had surgery sooner than non-MTC patients (22 v 37 days, p=0.02). Surgical MTC visits also produced less unnecessary preoperative testing per the ATA Guidelines (mean 0.1 v 0.2 test/patient, p=.05). Conclusion: In a physician-designed multidisciplinary center the evaluation of surgical thyroid nodule patients was more precise and efficient than in the traditional setting, with quantifiable advantages for both patients and physicians. Algorithmic preoperative evaluation increases quality outcomes and reduces time to definitive surgery especially for thyroid cancer patients.

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Predictors of Primary and Distant Site Surgery in Stage IV Colorectal Cancer Patients L.A. Uyeno,* R. Nelson, G. Singh, J. Garcia-Aguilar, J. Kim. *Surgery, City of Hope, Duarte, CA.*

Background: Operative management of primary tumor and distant metastases in stage IV colorectal cancer is highly variable and removal of asymptomatic primary tumors in the setting of distant disease remains controversial. The purpose of our study was to describe the patterns of surgery in stage IV colorectal cancer patients in a US population-based cohort and explore patient and tumor characteristics associated with treatment and survival. Methods: Stage IV colorectal cancer patients in Los Angeles County from 2000 to 2006 were identified using the LA County Cancer Surveillance Program registry. The cohort included 2,956 patients (2,211 stage IV colon and 745 stage IV rectal cancers). Cox proportional hazard models were used to estimate survival. Treatment was categorized as primary surgery, distant site surgery, or chemotherapy only. Multivariate logistic regression was used to identify patient and tumor variables associated with treatment. Results: Greater than 65% of the stage IV colorectal cohort had primary tumor surgery of which 51% had chemotherapy. Only 4.5% had surgery to remove distant disease. Patients who had chemotherapy only and no surgery was 15%. Median survival of primary surgery, distant surgery, or chemo only was 14, 21, and 11 months. Multivariate Cox regression revealed that primary surgery and distant surgery had a decreased risk of death compared to no surgery (HR= 0.4 p<.0001, HR=0.7 p<.004). Logistic regression identified predictors associated with treatment. Patients >65 years (p<.003); low socioeconomic status (p<0.05); and rectal tumors (p<.0001) were less likely to have surgery of the primary tumor. Female gender (p<.0001) and primary tumor surgery (p<.0001) were predictors for distant site surgery whereas age>65 years (p<.0001) had a negative association. Conclusions: Our study of stage IV colorectal cancer patients suggests that the majority of stage IV patients with distant disease have surgery, but less than 5% have surgery for distant disease. Although survival of stage IV colorectal patients is improved with surgery, increasing age, low socioeconomic status, and rectal tumors are negative predictors for undergoing surgery.

Univariate and Multivariate Cox Proportional Hazard Model Results

			Univariate					Multivariate				
		N	HR	Lower CI	Upper CI	p-value	overall p-value	HR	Lower CI	Upper CI	p-value	MVA p-value
Age (years)	<55	618	1.00				<.0001	1.00				<.0001
	55-64	640	1.19	1.04	1.35	0.009		1.18	1.04	1.35	0.01	
	65-74	717	1.42	1.25	1.60	<.0001		1.37	1.21	1.56	<.0001	
	>75	981	2.00	1.79	2.25	<.0001		2.24	1.96	2.56	<.0001	
Sex	Male	1502	1.00				0.6040	1.00				0.3165
	Female	1454	0.98	0.91	1.06	0.6042		0.96	0.89	1.04	0.3165	
Primary Site	Colon	2211	1.00				0.0064	1.00				0.1088
	Rectum	745	0.88	0.81	0.97	0.0069		0.92	0.83	1.02	0.1088	
SES Status	Highest	586	1.00				0.0320	1.00				0.0509
	Middle	1898	1.15	1.03	1.27	0.0090		1.16	1.04	1.29	0.0060	
	Lowest	461	1.17	1.02	1.34	0.0229		1.17	1.01	1.35	0.0394	
	Unknown	11	1.54	0.82	2.89	0.1746		1.16	0.62	2.19	0.6456	
Race/Ethnicity	White	1484	1.00				<.0001	1.00				0.0049
	Black	472	1.19	1.07	1.33	0.0021		1.15	1.02	1.29	0.0176	
	Hispanic	600	0.82	0.74	0.91	0.0002		0.95	0.85	1.06	0.3625	
	Asian	390	0.86	0.76	0.97	0.0141		0.88	0.77	0.99	0.0396	
	Unknown	10	0.99	0.52	1.91	0.9825		0.89	0.46	1.72	0.7306	
Tumor Size	0-5cm	1053	1.00				<.0001	1.00				0.0374
	>5cm	1013	1.02	0.93	1.12	0.6650		1.02	0.92	1.12	0.7586	
	Unknown	890	1.65	1.50	1.82	<.0001		1.17	1.03	1.33	0.0127	
Grade	I	124	1.00				<.0001	1.00				<.0001
	II	1566	1.12	0.91	1.39	0.2921		1.26	1.02	1.57	0.0358	
	III	826	1.37	1.10	1.71	0.0045		1.57	1.26	1.97	<.0001	
	IV	26	2.04	1.29	3.22	0.0023		2.66	1.67	4.23	<.0001	
	Unknown	414	1.65	1.31	2.08	<.0001		1.19	0.94	1.50	0.1467	
Lymph Node	Negative	647	1.00				<.0001	1.00				<.0001
	Positive	1516	1.28	1.15	1.42	<.0001		1.54	1.38	1.73	<.0001	
	Unknown	793	2.24	1.99	2.51	<.0001		1.38	1.20	1.58	<.0001	
Chemotherapy	No	1519	1.00				<.0001	1.00				<.0001
	Yes	1437	0.49	0.46	0.53	<.0001		0.55	0.50	0.60	<.0001	
Primary Surgery	No	1022	1.00				<.0001	1.00				<.0001
	Yes	1934	0.47	0.43	0.51	<.0001		0.55	0.50	0.60	<.0001	
Distant Surgery	No	2821	1.00				<.0001	1.00				0.0021
	Yes	135	0.55	0.44	0.68	<.0001		0.71	0.57	0.88	0.0021	

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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Analysis of the Learning Curve in Two Italian Centers using the Risk-adjusted Sequential Probability Ratio Test M. Deraco,[1] S. Virzì,[2] D. Baratti,[1]* S. Bonomi,[2] D. Iusco,[2] A. Grassi,[2] S. Kusamura.[1] *1. Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; 2. Bentivoglio Hospital, Bentivoglio (BO), Italy.*

INTRODUCTION Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a technically demanding and potentially morbid treatment option successfully used in the management of peritoneal surface malignancies. The learning curve of this complex procedure has never been thoroughly investigated. We performed the risk adjusted sequential probability ratio test (RA-SPRT) to assess the learning curve in a tertiary referral center (TRC) and the effect of surgical tutoring on a community hospital (CH). METHODS Two prospective databases including all patients operated on since 1995 at the TRC and since 2003 at the CH were reviewed. Technical support and surgical tutoring were given by the TRC to the CH surgical team during the early phase of its experience. CRS and closed abdomen HIPEC with cisplatin and mitomycin-C/doxorubicin were performed in both centers according to the same highly standardized protocol. Study outcomes were failure to perform an optimal cytoreduction, G3-5 morbidity (NCI-CTCAE.v3) and operative mortality. RA-SPRT curves were generated for both centers. The level of acceptable odds ratio for each outcome was determined on the basis of literature data. The risk-adjustment was made by a logistic regression model. RESULTS 641 procedures were performed: 432 at the TRC and 209 at the CH. In the entire cohort, incomplete cytoreduction, G3-5 morbidity, and operative death rates were respectively 8.4%, 30.1%, and 3.9%. Incomplete cytoreduction, G3-5 morbidity, and operative death rates were 10.1%, 29.4%, and 2.6% at the TRC, and 4.8%, 31.6%, and 7.6%, respectively, at the CH. At the TRC, the learning curve reached the level of acceptable odd ratios for incomplete cytoreduction, G3-5 morbidity and operative death at 141, 158, and 144 cases, respectively. At the CH, the breaking points were located at 126, 134, and 60 cases. Conclusions: Between 140 to 150 procedures are required to perform CRS and HIPEC safely and to assure acceptable rates of optimal cytoreduction. Surgical tutoring on inexperienced teams may shorten the learning curve.

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Evaluation of Quality of Care for Colorectal Cancer Patients in Japan: An Analysis Using the Clinical Database M. Ishiguro,[1]* K. Sugihara,[1] T. Higashi,[2] T. Sobue.[3] *1. Tokyo Medical and Dental University, Graduate School, Tokyo, Tokyo, Japan; 2. The University of Tokyo, Graduate School of Medicine, Department of Public Health / Health Policy, Tokyo, Japan; 3. Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan.*

Introduction: In 2005, the Japanese guidelines for the treatment of colorectal cancer was published to promote the standards of care for colorectal cancer (CRC). To assess the current status of care for CRC patients and to improve the quality of the care, we developed a set of 45 process-of-care quality indicators (QIs). The aim of this study is to evaluate the status of CRC care in Japan by using the QIs. Methods: We applied the QIs to the data from the clinical database collected by a study group of the 18 facilities. The database included the patients who received curative surgery for CRC from 1997 to 2000. Results: A total of 4824 patients were studied. Of the 45 QIs, 5 QIs were able to measure using the database. Substantial variation in adherence scores was seen across the QIs (52-92%). In particular, the patients who received adequate lymph node dissection recommended in the guidelines were 56% of Stage II, III CRC patients. The patients who received adjuvant chemotherapy were 52% of Stage III CRC patients. Wide variation across the facilities was observed in these 2 QIs. On the other hand, the adherence score of describing the pathological findings of the surgically resected specimens was high (92%), and variation across the facilities was small. The observation that many items remained missing in the database disclosed importance to improve the quality of the database. Conclusions: We assessed the status of CRC care using the originally developed QIs. The 5 QIs could be measured from the database, revealing substantial variation in adherence scores was seen across the facilities. Measuring QIs by using the database was efficient and useful to overview the QIs from multiple facilities. Periodic assessment is essential to the improvement of the quality of care and the quality of the database.

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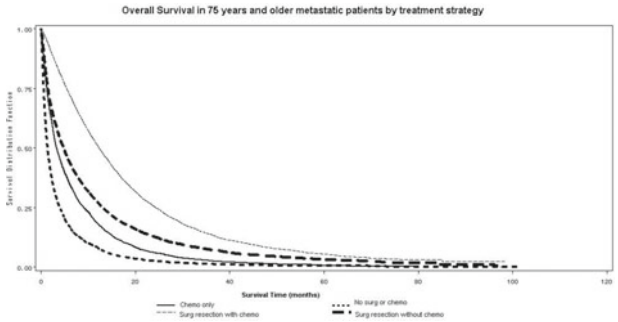
Defining the Role of Primary Tumor Resection and Chemotherapy in Patients 75 and Over Presenting with Metastatic Colon Cancer L.T. Li,[1]* J.N. Cormier,[2] B.W. Feig,[2] N.J. Petersen,[3] S. Sansgiry,[3] A. Artinyan,[4] D.H. Berger,[4] D.A. Anaya.[4] *1. Michael E. DeBakey Department of General Surgery, Baylor College of Medicine, Houston, TX; 2. MD Anderson Cancer Center, Houston, TX; 3. HSR&D Center of Excellence, Houston, TX; 4. Baylor College of Medicine And The Michael E DeBakey Veterans Affairs Medical Center, Houston, TX.*

INTRODUCTION: The management of patients presenting with synchronous metastatic colon cancer (mCC) with the primary tumor in place typically includes primary tumor resection and chemotherapy. The utilization patterns and role of this treatment strategy is not well defined for the elderly. We sought to characterize and compare the use of primary tumor resection and chemotherapy based on age, and to evaluate the impact on survival of this treatment as compared to other strategies. METHODS: A retrospective cohort analysis was done using the National Cancer Database. Patients presenting with mCC were identified (1998-2002), and categorized in two age groups: Young (50 – 74) and Oldest (>= 75). The primary and secondary outcomes were primary tumor resection and chemotherapy utilization rates and survival, respectively. Annual and overall rates of primary tumor resection and chemotherapy were calculated and compared. Survival analysis using the Kaplan-Meier method was done for the different treatment strategies in the oldest population. RESULTS: The study sample consisted of 60,521 patients; 43,901 (73%) had primary tumor resection and 32,151 (53%) received chemotherapy. Despite no changes in the use of chemotherapy, there was a significant drop in the use of primary tumor resection over time (75% vs. 70%, P<0.001). The oldest patients were less likely to have primary tumor resection (67% vs. 76%, P<0.001) and to receive chemotherapy (39% vs. 67%, P<0.001). Overall survival (OS) for the oldest population was determined by treatment strategy (Figure); median OS was highest for those having primary tumor resection and chemotherapy (12.3 months) as compared to those having resection only (4.8 months) those receiving chemotherapy only (3.3 months) and those with no treatment (1.3 months) (P=<0.001). CONCLUSIONS: Patients over 75 years presenting with mCC are less likely to have primary tumor resection and chemotherapy. Despite advanced age, the use of this treatment strategy is associated with improved

survival. Future emphasis must be placed on providing this standard of care to patients over 75y who are adequate surgical candidates.



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Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis: Analysis of Postoperative Morbidity and Mortality from a High Volume Center P. Shen,* J. Gahagan, J.H. Stewart, K. Votanopoulus, K. Swett, E.A. Levine. *Dept Gen Surg, Surgical Oncology Service, Wake Forest University Health Sciences, Winston-Salem, NC.*

Introduction: Cytoreductive Surgery (CS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for peritoneal carcinomatosis (PC) secondary to select tumor types has been associated with improved survival and is undergoing increased utilization in the surgical oncology community. However it is a procedure associated with significant morbidity and potential for mortality. Methods: A systematic review of postoperative outcomes was performed. Patients treated from February 1995 to April 2011 were analyzed using a prospectively maintained database. Index morbidity/mortality outcomes were determined and correlated with preoperative/intraoperative variables. Results: Seven hundred fifty one patients undergoing 813 procedures with PC from various histologies were examined. The median surgery length and blood loss per procedure was 8.1 (range: 0.2, 20.0) hrs and 500 (range: 50,6000) cc's, respectively, with bowel anastomoses performed in 59.9% of cases. Overall morbidity rate was 57.1% with the following complication grade distribution: I, 12.8%; II, 22.3%; III, 18.2%; IV, 3.8%. The incidence of fistula/perforation/leak, hematologic toxicity, reoperations, and readmissions (within 30 days) was 11.0%, 15.9%, 14.2%, and 11.8%, respectively. Mortality rate was 6.5% with 35.8% of deaths associated with gastrointestinal perforations/leaks. Multivariate analysis of perioperative factors found diabetes (p=0.01), ECOG 2-4 vs 0-1 (p=0.01), Resection status 2 vs 0/1 (p=0.006), higher number of anastomoses (p=<0.001), and ten year increase in age (p=0.007) to be significantly associated with morbidity, while smoking (p=0.03), ECOG 2-4 vs 0-1 (p=0.006), Resection status 2 vs 0/1 (p=0.05), and ten year increase in age (p<0.001) were significantly associated with mortality. Conclusions: CS with HIPEC for PC is a high risk procedure even when performed at a high volume center. Careful evaluation of functional status, co-morbidities, age, and tumor burden in patient selection is important to decrease adverse postoperative outcomes.

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Age-Related Morbidity and Mortality Outcomes following Gastric Surgery: An Analysis of 13,799 Patients from the National Inpatient Sample Database (NISD) A. Karkar,* S. Patil, R.S. Chamberlain. *Saint Barnabas, Livingston, NJ.*

Introduction: Surgery is the only curative intervention for gastric cancer but is associated with significant morbidity and mortality, particularly in the elderly. This study aims to assess age-related clinical outcomes following gastrectomy across all age groups to allow more precise preoperative surgical risk stratification. Methods: Between 2004 and 2008, clinicopathological and outcomes data was collected from 13,799 gastrectomy patients from the NISD. Eight age groups were compared for total gastrectomy (TG) and partial gastrectomy (PG). Categorical data was compared using the Chi square test and continuous data using Student's t test. Results: Among 13,799 patients, 23.7% underwent TG and 76.3% underwent PG for gastric cancer. Overall, twice the number of males than females received TGs, whereas equal numbers received PGs. Gastric carcinoma was the most common indication for TGs especially in the 9th decade (100%). Non-elective admissions were common for PGs (41%) as compared to TGs (21.2%). The mean preoperative and total hospital length of stay trended upward with advancing age for both TG and PG (p <0.001). Overall mortality was 7.6% for TG and 6.4% for PG, increasing with age for both groups (p <0.001). The most common comorbidities were HTN and fluid and electrolyte imbalances. The most common complications for TG patients were respiratory (13.8%) and gastrointestinal (GI) (12.5%), whereas for PG, GI complications (10.7%) and bile duct fistulas (7.2%) were most common. The number of TGs increased over the 5-year study period, with the highest percentage change in the 4th decade of life (1500%). The number of PGs performed decreased overall, especially in patients <60 years, but increased in patients >80 years with the highest percentage change in patients >90 years (13%). Conclusions: TG is performed more commonly now, especially in the elderly and male populations and is associated with increased mortality compared to PG. Its most common indication at all ages is gastric carcinoma. The increasing number of TGs for gastric cancer likely reflect increased incidence of body and cardiac lesions.

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Improving Colorectal Cancer (CRC) Surveillance May Lead to Higher Rates of Liver Metastasectomy for Recurrent CRC: An Ontario Population-based Study L. Ruo,* S. Orr, M. Simunovic. *McMaster University, Hamilton, ON, Canada.*

INTRODUCTION: Evolving surgical standards encourage increasingly aggressive approaches to CRC liver metastasectomy. Few epidemiologic studies provide data addressing rates and patterns of recurrence or surgical resection of liver metastases in a population-based cohort of Stages I-III treated CRC patients. METHODS: LHIN4 (population 1.3 million) is the largest of 14 health administration LHINs in Ontario. Surgical care is delivered at 10 community and 2 teaching hospitals, and a regional cancer centre provides nearly all chemotherapy and all radiotherapy for cancer patients. We evaluated patterns of recurrence with liver metastases and surgical treatment in a population-based cohort of patients treated for Stages I-III CRC. Chart abstraction provided data elements on clinician visits and investigations utilized (CEA, US, CT, MR) to diagnose recurrence and metastases. RESULTS: From November 1, 2005 to March 31, 2006, 265 patients underwent surgical resection for Stages I-III CRC. Among these patients, there were 59 Stage I, 99 Stage II, and 107 Stage III. The number of patients who developed liver metastases among these same groups was 2 (3.4%), 7 (7.1%) and 32 (30%), respectively. Surveillance following CRC resection was poor; 10 (24%) had annual liver imaging by CT or US, 9 (22%) had annual CEA, and only 2 (5%) had both types of surveillance investigations in the first three years of follow-up. Only 9 of 41 patients with liver metastases were evaluated by a liver surgeon, and 6 proceeded to hepatic metastasectomy. Patients not referred for surgical consultation were older (median age 72 vs. 62 yrs) and had higher serum CEA levels (754 vs. 197 ug/L). CONCLUSIONS: We provide recent population-based data on the evaluation and management of resected Stage I-III CRC patients who develop liver metastases. Interventions to improve quality of clinical care should target optimization of surveillance strategies and referral for multidisciplinary assessment, including surgical consultation.

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National Trends in Surgical Management of Cystic Lesions of Pancreas B.C. Shah,* L.M. Smith, A. Sasson, Q.P. Ly, C. Are. *Surgery, University of Nebraska Medical Center, Omaha, NE.*

Introduction: This study aimed at finding national trends for operative management of cystic lesions of the pancreas. Methods: The Nationwide Inpatient Sample (NIS) database was queried (1993 to 2005) to look at trends in operative management and discharge status for cystic lesions of pancreas.Results: A weighted total of 70,488 adult patients had a primary diagnosis of cystic lesion of pancreas between 1993 and 2005. The overall mortality was stable over the study period (1.2%-2.7%). The proportion of patients with a cystic lesion that underwent a pancreatectomy grew from 4.6% in 1993 to 9.4% in 2005 (p=0.0001). Radical pancreatectomy increased from 0.4% to 1.5%, distal pancreatectomy increased from 3.2% to 6.1% and other procedures grew from 1.0% to 1.8% (p=0.0001). Univariate Analysis showed significant associations between having a prancreatectomy with age > 70, female sex, hospital size, teaching hospital, hospital location, length of stay >10 days, elective admission type,and not having diabetes. Multivariate analysis (Table 1) From

1993 to 1999 patients with cystic pancreatic lesions was significantly less likely to have a procedure than in 2005. Patients older than 70 years were 28% less likely to have a procedure than those with age less than 70. Females were 2 times more likely to have a procedure than males. Patients with diabetes were less likely while those with length of stay of more than 10 days were more likely of having a pancreatectomy. Conclusion: There is an increasing trend in operative management for cystic lesions of the pancreas.

Table 1. Multivariate model of probability of a procedure compared to non-procedure, using a logistic regression model.

		Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Year	1993	0.37	0.24	0.59	0.0003
	1994	0.50	0.33	0.76	
	1995	0.59	0.41	0.87	
	1996	0.50	0.33	0.76	
	1997	0.52	0.35	0.79	
	1998	0.56	0.37	0.84	
	1999	0.62	0.43	0.90	
	2000	0.71	0.49	1.04	
	2001	0.53	0.36	0.78	
	2002	0.93	0.66	1.30	
	2003	0.72	0.50	1.04	
	2004	0.78	0.54	1.15	
	2005	1	-	-	
Age Group	<70 years	1	-	-	0.0055
	70+ years	0.72	0.58	0.91	
Sex	Male	0.51	0.45	0.59	<0.0001
	Female	1	-	-	
Admission type	Non-routine	0.17	0.14	0.20	<0.0001
	Routine	1	-	-	
Hospital size	Large	1.32	1.10	1.59	0.0035
	Small/ mediaum	1	-	-	
Hospital status	non-teaching	0.68	0.57	0.82	0.0001
	teaching	1	-	-	
Length of stay	10 days or less	1	-	-	<0.0001
	>10 days	2.29	1.97	2.66	
Diabetes	No	1.50	1.22	1.84	0.0001
	Yes	1	-	-	
Discharge Disposition	Routine	1.06	0.59	1.89	0.0007
	Other facility	0.55	0.29	1.04	
	Home health	1.06	0.59	1.97	
		Died	1	-	-

P323

Nurse Navigator Implementation at a Comprehensive Breast Center: Relating a Quality Improvement Initiative with Access to Care and Patient Satisfaction J. Linebarger,* M. Basu, M. Amin, S. Patterson, C. McCarthy, H. Pinkerton, K. Gress, R. Tarpley, M. Newell, S. Gabram. *Emory University Hospital, Atlanta, GA.*

Introduction: The National Accreditation Program for Breast Centers (NAPBC) requires an established patient navigation process. We sought to objectively evaluate the introduction of a Breast Nurse Navigator (BNN) at an academic, tertiary referral, comprehensive breast center by measuring the effect on timeliness of care and assessing patient satisfaction. Methods: The BNN was introduced in July, 2010. All breast cancer patients in the study were internally diagnosed with Stage I-III disease and were identified by retrospective cancer registry and chart review. Patients diagnosed and managed from January to June, 2010 were compared to patients diagnosed and managed with the assistance of BNN services from January to June, 2011. Time intervals were recorded from date of biopsy to date of: pathology report, consultation for definitive care, and first treatment. All navigated breast cancer patients from January to June, 2011, received a patient satisfaction survey including questions to quantify satisfaction with timeliness and coordination of care. Results: Overall, 96 patients met inclusion criteria for analysis of timeliness, 55 (57%) in 2010 and 41 (43%) in 2011. Time intervals from biopsy to diagnosis, consultation, and first treatment in 2010/2011 were 3/3, 9/9, and 28/26 days, respectively. Among the subset of 66 patients diagnosed after referral for diagnostic evaluation from a primary care provider, time to first treatment was 32/26 days in 2010/2011 (n=33/33; p=0.11). Twenty-one patients (27%) responded to the satisfaction survey. Patients reported a high rate of satisfaction or extreme satisfaction with time to first appointment (100%), timelines of care (86%), BNN assistance (95%), and team's ability to coordinate care (95%). (Table 1) Conclusion: Timeliness of consultation for definitive care and first treatment did not change following introduction of BNN services; however, a high degree of patient satisfaction occurred with the reported timeliness intervals. Patients were generally extremely satisfied with BNN assistance and the team's ability to coordinate care.

Table 1. Breast Cancer Patient Satisfaction Survey: Jan-Jun, 2011.

Response	Time to first appointment.	Timeliness of your care.	Nurse navigator in assisting you.	Team's ability to coordinate care.	Overall clinical care received.
Tally (n=21; 27% response rate)					
ED	-	-	-	-	-
D	-	-	-	-	-
N	-	2	1	-	-
S	8	2	4	5	4
ES	13	16	16	15	17
DNA	-	1	-	1	-
Percent of Responders Who Were Satisfied or Extremely Satisfied					
S or ES	100%	86%	95%	95%	100%

ED=Extremely Dissatisfied, D=Dissatisfied, N=Neutral, S=Satisfied, ES=Extremely Satisfied, DNA=Did Not Answer.

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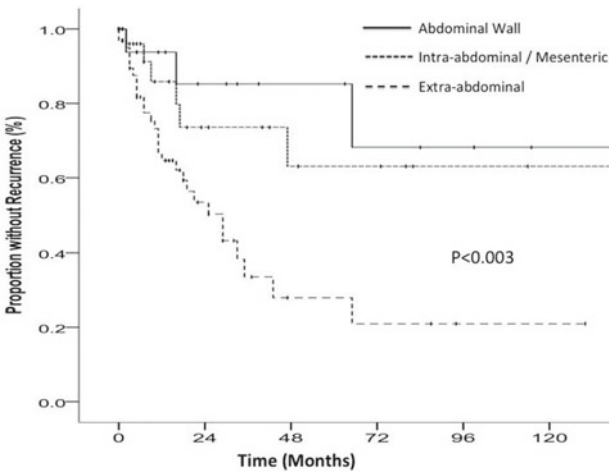
Management of Desmoid Tumors: Incidence of Recurrence and Factors Associated with Recurrence-free Survival P.D. Peng,* P. Kneuertz, A. Firoozmand, J. Cameron, J. Herman, C. Wolfgang, B. Edil, R. Schulick, M. Choti, R. Anders, T.M. Pawlik. *Johns Hopkins Hospital, Baltimore, CA.*

Background: Desmoid tumors are rare locally-aggressive mesenchymal tumors that arise from soft tissue. We sought to define the incidence of recurrence, as well as factors associated with recurrence-free survival, in a large cohort of patients (pts). Methods: Between 1985-2011, 139 pts with pathologically confirmed desmoid tumors were identified from a single institutional database. Clinicopathological data were evaluated with univariate and multivariate analyses to identify factors associated with recurrence-free survival. Results: Among the 139 pts, most were female (70%) and median age was 35 years. Most pts presented with a symptomatic (83%) and solitary (93%) lesion. Median tumor size was 7 cm (2-34 cm); tumor locations were extremity (32%), mesenteric (24%), abdominal wall (18%), thoracic (16%), and head/neck (7.2%). Primary treatment included resection alone (68%), resection+medical therapy (9%), resection+radiation (6%), medical therapy alone (5%), or observation (12%). Surgical margins were negative (R0) (47%), microscopically positive (R1) (7%), and grossly positive (R2) (14%); 20 (14%) pts had unknown margin status. Post-operative morbidity was 17% with no mortality. Overall median and 5-year recurrence-free survival was 47 months and 50%, respectively. With median follow-up of 22 months, 38 (33%) pts recurred with a mean time of 11 months. Residual microscopic (R1, HR= 3.2; p=0.03) or macroscopic (R2, HR=3.7; p=0.001) disease was associated with a higher risk of local recurrence. In addition, pts with an extra-abdominal desmoid had over a four-fold increased risk of recurrence (HR=4.5; p=0.01) (Fig). Medical or radiation therapy was not associated with risk of recurrence. Among pts who recurred, 31 (82%) underwent repeat surgical resection; 16 out of 31 pts re-recurred. Conclusion: Up to one-third of patients treated for a desmoid tumor experienced a recurrence. While medical or radiation therapy was not associated with recurrence-free survival, extra-abdominal location and residual disease at the surgical margin were both associated with more than a three-fold increased risk of recurrence.



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Safety and Efficacy of Brachytherapy Delivered via Mesh Implantation for Locally Advanced Sarcomas J. Wang,* P.M. Devlin, J. Hansen, E.H. Baldini, J. Ready, D.J. Sugarbaker, M.M. Bertagnolli, C.P. Raut. *Surgical Oncology, Brigham and Women's Hospital, Boston, MA.*

Background Locoregional recurrence rates of up to 50% are observed following macroscopically complete resections of deep cavity soft tissue sarcomas (STS). Brachytherapy (BRT) delivered via catheters implanted during surgery results in local control rates of 90% following resection of high grade extremity and trunk STS, but there are technical limitations for this approach in deep cavities. The safety and efficacy of permanent BRT delivered via mesh implantation (mesh BRT) following resection of deep cavity STS have not been reported. **Method** All STS patients treated with mesh BRT from 2000-2010 were prospectively followed. ^{125}I seeds (0.25-0.60 Ci, half-life 60d) contained within polyglactin suture were sewn into polyglactin mesh and spaced 1 cm apart. The flexible mesh implant was contoured to the surface area of the closest margin after intraoperative margin assessment by a pathologist. **Results** Fifty STS patients underwent treatment with radical surgery and mesh BRT. Disease was primary in 20% and recurrent in 80%. External beam radiation therapy was delivered preoperatively (46%), postoperatively (4%), or both (6%). Patient and tumor characteristics are listed in Table 1. The primary indication for BRT was close/positive margin (78%), commonly along a major vessel or nerve (74%). With a median follow-up of 26 months, recurrences were observed within the field of the mesh in 12%. Recurrences beyond the field of the mesh (including distant metastases) but not within the field of the mesh were observed in 64%. Postoperative complications were noted in 48%, including wound infection/seroma/hematoma (n=11), small bowel obstruction/ileus (2), ascites (2) and enterocutaneous fistula (1). No vascular disruption or neuropathy was noted, though 3 patients developed DVT/PE. **Conclusions** Permanent mesh BRT achieves local control rates comparable to temporary catheter BRT following resection of locally advanced STS in cavities where the latter is not commonly used. Although, postoperative complication rates are high, mesh BRT may be safely placed against close margin surfaces along vessels or nerves where more radical surgery may be debilitating.

Age (median, range)	52.3 (15.7-85.7)
Gender	
Female	24 (48%)
Male	26 (52%)
Disease Status	
Primary	10 (20%)
Recurrent	40 (80%)
Location	
Abdomen/Pelvis/Retroperitoneum	30 (60%)
Thoracic Cavity	9 (18%)
Trunk	4 (8%)
Extremity	7 (14%)
Histology	
Liposarcoma	17 (34%)
Leiomyosarcoma	9 (18%)
Spindle cell sarcoma, not otherwise specified	6 (12%)
Synovial sarcoma	5 (10%)
Malignantperipheral nerve sheath tumor	4 (8%)
Myofibroblastic sarcoma	3 (6%)
Epithelioid sarcoma	2 (4%)
Hemangiopericytoma	1 (2%)
Osteosarcoma	1 (2%)
Chondrosarcoma	1 (2%)
Fibromyxoid sarcoma	1 (2%)

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Post Radiation Stress Fractures after Treatment for Soft Tissue Sarcomas J. Seinen,[1]* P. Jutte,[2] R. Van Ginkel,[1] B. Pras,[3] H. Hoekstra.[1] *1. University Medical Center Groningen, department of Surgical Oncology, Groningen, Netherlands; 2. University Medical Center Groningen, department of Orthopedics, Groningen, Netherlands; 3. University Medical Center Groningen, department of Radiation Oncology, Groningen, Netherlands.*

OBJECTIVE The combined treatment modality isolated limb perfusion (ILP), delayed surgery and adjuvant radiotherapy (RT) is a successful limb saving treatment for locally advanced soft tissue sarcomas (STS), but some patients are at high risk for developing a postradiation stressfracture (PSF) with delayed bone healing. Treatment is challenging and little is known about optimal treatment. Therefore, treatment and outcome of patients with a PSF after ILP was studied. METHOD Out of 113 consecutive patients undergoing ILP and delayed surgery between 1991 and 2010, 43 STS were located at the thigh, of which 29 patients received adjuvant RT due to marginal margins, of median 70 (60-70) Gy (in fractions of 2 Gy). Of the latter group, 5 patients (17%) developed a PSF after median 56 (1-91) months (Fig 1). Two patients received RT twice for a primary tumor as well as a local recurrence. Twenty-nine STS were located at the lower leg, 16 patients received RT of median 66 (60-70) Gy, and 1 patient (6%) developed a PSF. All PSF's developed in the booster area for the tumor bed of median 20 (10-20) Gy. RESULTS All patients with a femoral fracture were treated with internal fixation. The patient with a tibia fracture had a concurrent nonhealing postradiation wound which necessitated an amputation. None of the patients with internal fixation reached consolidation of the bone. Their median survival was 19 (1-126) months, 3 patients died due to lung metastases within 1,5 year. The other 2 patients are alive 9 and 10 years after fracture treatment without evidence of disease. One patient received, after 2 broken intramedullary nails, reconstruction of the proximal femur with an endoprosthesis with good functional outcome. The other patient has moderate mobility due to pseudoarthrosis as consequence of the internal fixation, but refuses an endoprosthesis. CONCLUSION Almost one fifth of patients with STS of the thigh treated with ILP, surgery and RT developed a PSF. Due to a poor prognosis of these STS patients, non extensive treatment for the fracture is required to enable mobilisation and reasonable quality of life. For the long survivors an endoprothesis might be indicated and discussed with the patient.

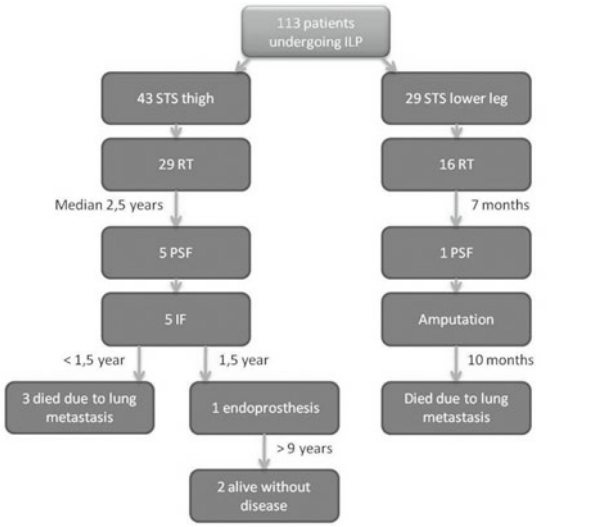

Figure 1. Overview patients developing a post radiation stress fracture

Figure 1. Overview of patients developing a post radiation stress fracture

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Elevated Blood Neutrophil-to-Lymphocyte Ratio is a Predictor of Postoperative Disease Recurrence in Gastrointestinal Stromal Tumor (GIST) D. Perez,[1]* R. Baser,[2] C. Antonescu,[3] S. Singer,[1] R. DeMatteo.[1] *1. Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; 2. Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; 3. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: The neutrophil-to-lymphocyte ratio (NLR) is hypothesized to reflect the systemic inflammatory response created by a tumor and is possibly predictive of tumor biology. Whether NLR has prognostic value in GIST remains unclear. Methods: Clinicopathological data were reviewed for patients with a primary localized GIST who underwent resection between 1995 and 2011. Preoperative blood tests were used to calculate NLR, which was defined as elevated if equal or higher 5. The 2-year and 5-year recurrence-free survival (RFS) was predicted based on a previously validated established nomogram. The actual RFS was not included in this analysis due to variable use of adjuvant imatinib in this cohort. Cox regression modeling was conducted to analyze for prognostic factors. Results: We identified a total of 335 GIST patients who underwent attempted curative resection at our institution. There

were 53 patients (16%) who had an elevated NLR preoperatively. High NLR was associated with older age (P = 0.01), male gender (P = 0.02) and tumor size (P = 0.04). The predicted 2-year RFS difference between patients with a high and low NLR was small (84% and 89% respectively) but statistically significant (P = 0.001). The estimated 5-year RFS for patients with high NLR was 54% and 65% in the low NLR group (P = 0.002). In contrast, the absolute neutrophil and lymphocyte values as well as the white blood cell count were not associated with the predicted RFS. Conclusion: The preoperative NLR is a potential prognostic marker for recurrence in GIST. The systemic inflammatory response to primary GIST or other patient-specific immunologic characteristics may predispose to tumor recurrence.

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Surgical Resection of Duodenal Gastrointestinal Stromal Tumors (GIST): Short- and Long-term Outcomes Relative to Extent of Operation F.M. Johnston,[1]* P. Kneuertz,[1] W. Hawkins,[2] D. Sanford,[2] B. Edil,[1] R. Schulick,[1] M. Choti,[1] K. Hirose,[1] J. Cameron,[1] T.M. Pawlik.[1] *1. Johns Hopkins Hospital, Baltimore, MD; 2. Surgery, Washington University in Saint Louis, Saint Louis, MO.*

Introduction: Duodenal Gastrointestinal Stromal Tumors (dGIST) are rare and account for < 5% of all GIST cases. As such, surgical management of dGIST has not been well characterized. We sought to define the short and long-term outcome of patients undergoing resection of dGIST with a particular emphasis on the impact of pancreaticoduodenecomy (PD) vs. local resection (LR). Methods: Between 1994-2011, 54 patients who underwent surgical resection of pathologically confirmed dGIST were identified from the databases of two major centers. Clinical and pathological data were evaluated to identify factors associated with recurrence and overall survival. Results: Most patients were male (n=33; 61%) and median age was 55 years. Symptoms on presentation included pain (24%), occult bleeding (22%), gross bleeding (20%), and obstruction (6%). The majority of pts had a solitary tumor (91%). dGIST location was D1/D2 (n=34, 61%) and D3/D4 (n=21, 39%). At surgery, 25 (46%) pts underwent LR while 29 (54%) underwent PD; LR was performed more commonly for D3/D4 lesions (72%) (P<0.001). On final pathology, median tumor size (LR, 4 cm vs. PD, 5 cm), mitosis/50 HPF (≤ 5: LR, 76% vs. PD, 72%), and margin status (R0: LR, 92% vs. PD, 90%) were similar in both groups (all P>0.05). Morbidity (LR, 24% vs. PD 55%) and median length of stay (LR, 6 d vs. PD, 11 d) were higher following PD (both P<0.05). Some patients were treated with adjuvant gleevec (17%) or sutent (1%). 5-year overall survival was 58%; 10 (19%) patients recurred (local, n=2; distant, n=5; both, n=3). Factors associated with disease recurrence included tumor size >5cm, multifocal disease, and NIH risk classification (all P≤0.05) (Table). Overall median survival was 52 months for patients undergoing LR vs. 115 months for PD (P=0.38). Conclusion: Surgeons operating on pts with dGIST need to be skilled in PD as up to one-half required a PD due to tumor location. Biologic factors, rather than the specific procedure, dictated long-term outcome. The extent of operation for dGIST should be determined by anatomic location and the ability to achieve negative margins.

Impact of Clinicopathological Factors on Recurrence-Free Survival

		Recurrenc Free Survival
Variable	Odds Ratio	P-Value
Age >55	0.96	0.96
Female Sex	0.81	0.76
Tumor Size >5 cm	4.73	0.05
Mitotic Number/50 HPF ≤ 5 6-10 >10	 Reference 1.75 4.99	 0.44 0.06
AJCC/UICC Stage I Stage II Stage III	 Reference 8.10 5.51	 0.07 0.14
NIH risk classification Low Interediate/High	 Reference 7.67	 0.05
Site D1/D2 D3/D4	 Reference 0.88	 0.79
Multifocal Disease	5.03	0.02
Margin Status R0 R1	 Reference 2.83	 0.18
Gleevec/Sutent	3.00	0.09
Extent of Resection Limited Resection Whipple	 Reference 2.21	 0.32

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Prognosis of Malignant Solitary Fibrous Tumors: A Multi-center Study W.J. Van Houdt,[1]* A.J. Witkamp,[2] J. Van Gorp,[1] T. Van Dalen.[1] *1. Diakonessenhuis Utrecht, Utrecht, Netherlands; 2. University Medical Center Utrecht, Utrecht, Netherlands.*

Introduction: Solitary fibrous tumors are rare soft-tissue tumors with variable malignant potential. The majority of these tumors originate within the thoracic cavity, but they also occur in the central nervous system, pelvis, abdomen, soft tissues and muscles. We report the outcomes of solitary fibrous tumors treated in 5 centers in the Netherlands. Methods: Retrospective analysis was performed on patients with histologically-proven malignant solitary fibrous tumors diagnosed between 1998 and 2007. Kaplan Meier survival curves were constructed and differences were assessed by Log-Rank and Wilcoxon test. Results: 20 patients were identified with malignant solitary fibrous tumors. 14 patients were female, only 6 patients were male. Of these patients, 18 underwent surgical resection with curative intent, 2 tumors were irresectable. Only 1 patient was treated with adjuvant radiotherapy, no patients were treated with chemotherapy. Of all patients, 5 developed sooner or later distant metastases. A total of 7 tumors were located in the lungs or elsewhere in the thoracic cavity. All patients disease free survival (DFS) rates were 78% at 2 years and 46% at 5 years. All patients overall survival (OS) rates were 89% at 2 years and 62% at 5 years. Overall survival was not affected by post-operative radiotherapy, size of the tumor, age or sex of the patient. However, for solitary fibrous tumors located in the thoracic cavity, the overall survival was significantly lower (p<0,043) when compared to all other locations. Conclusions: In this retrospective multi-center study, we showed that prognosis of solitary fibrous tumors widely varies between different cases. Thoracic cavity-located tumors have worse prognosis when compared to tumors located elsewhere in the body.

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A Single Institution Experience Treating Children with Extraosseous Ewing Sarcoma W.S. Orr,* J.W. Denbo, C.A. Billups, J. Wu, F. Navid, B.N. Rao, A.M. Davidoff, M.J. Krasin. *St. Jude Children's Research Hospital, Memphis, TN.*

Introduction: Although substantial data are available on the treatment of Ewing sarcoma (ES) of the bone, little data exist on the treatment of extraosseous ES, particularly in pediatric patients. Therefore, we reviewed our experience in treating children with extraosseous ES. Methods: A retrospective analysis of all patients with extraosseous ES treated at our institution from June 1982 to August 2009. Results: Forty-six patients with extraosseous ES were identified. The median age at diagnosis was 13.8 years (range, 1.1 -24.8). The majority of patients were male and Caucasian. The most common site of primary tumor was the trunk (70%). Twelve patients (26%) had subcutaneous tumors. The median tumor size was 8 cm (range, 1-25). Six patients (13%) had metastatic disease at diagnosis. Eighteen patients received neoadjuvant chemotherapy. There was no evidence of significant differences between margin status with the site of tumor, tumor size, or the use of neoadjuvant chemotherapy. 59% of patients were alive at the time of analysis with a median follow-up from diagnosis of 15.3 years. Fifteen year estimates of survival and event free survival (EFS) for all patients were 53.3% ± 9.4% and 50% ± 9.1%, respectively. Stage was a significant predictor of outcome (p<0.001); 15-year estimates of survival and EFS for patients with localized disease were 61.4% ± 9.8% and 57.6% ± 9.7%, respectively. Among localized patients, subcutaneous ES was a significant predictor of survival (91.7% ± 9.4% vs. 47.2% ± 12.1% at 15 years; p=0.031). The outcome for patients with localized extraosseous ES (10-year EFS, 68.8 ± 8.4%) was similar to that previously reported for all ES patients treated on protocols at our institution (60.9 ± 4.9%; p=0.5). Excluding subcutaneous extraosseous ES, the 10-year EFS was even more similar (62.4% ± 10.6% for our study cohort). Conclusions: The outcome for patients with localized extraosseous ES was similar to that reported for all ES patients treated on protocols at our institution. Patients with subcutaneous ES had improved outcome compared to ES at other sites.

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A Multidisciplinary Approach Using Intraoperative Electron Radiation Therapy Improves Local Control in Retroperitoneal Sarcoma

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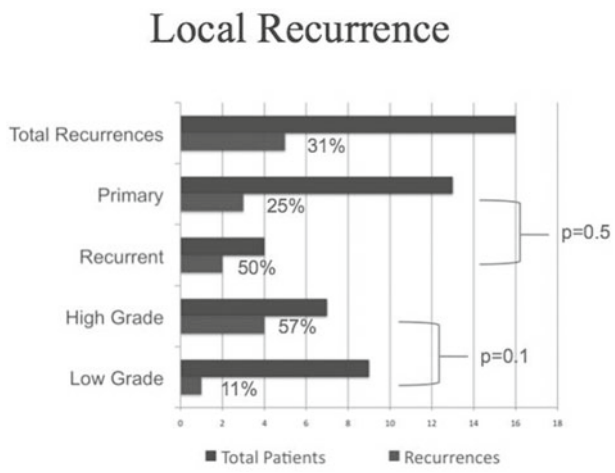
Introduction: Local recurrence rates in patients with retroperitoneal sarcoma (RPS) are high, ranging from 40-80%. Surgery remains the standard of treatment and no definitive studies exist describing the most efficacious way of to administer radiation. Intraoperative electron radiation therapy (IOERT) provides a theoretical advantage for access to the tumor bed with reduced toxicity to surrounding structures. The goal of this study is to evaluate the role of IOERT in high-risk patients. Methods: An IRB approved, single institution sarcoma database was queried to identify patients who received IOERT for treatment of RPS from February 2001 to January 2009. Decision for IOERT was made by a multidisciplinary team. Data was analyzed using the Kaplan-Meier method, Cox Regression and Fisher's Exact tests. Results: Eighteen patients (median age 50 years, 25-76) underwent tumor resection with IOERT (median dose 1250 cGy) for primary (n=13) and recurrent (n=5) RPS. Seventeen patients also received neo-adjuvant radiotherapy. Four patients died, two of which were peri-operative. The median follow-up of survivors was 3.6 years. Margins were R0 in 16 (89%) and R1 in 2 (11%). Eight high-grade and 10 low-grade tumors were identified. Median tumor size was 15 cm. Five patients (31%) developed a local recurrence (LR) in the radiated field, none in the setting of distant metastasis. Two patients with primary disease (25%) and three (50%) with recurrent disease developed a LR (p=0.5). Four patients with high-grade tumors (57%) and one with a low-grade tumor (11%) developed a recurrence (p=0.1). No difference was noted in OS or time to LR in patients with high vs. low-grade tumors (p=0.8, 0.2), multi-visceral resection (p=0.5, 0.2), or larger tumor size (p=0.9, 0.6). The two and five-year disease related OS rates were 100% and 72%. The two and five-year LR rates were 13% and 36%. Conclusions: Historically, RPS are associated with high rates of recurrence. Using a multidisciplinary approach we have achieved low local recurrence rates in our high-risk patient population indicating that IOERT may play an important role in managing these patients.



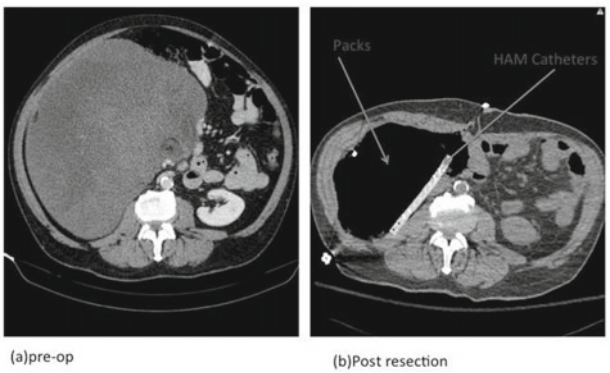
P332

Post-Operative Brachytherapy via Intraoperatively-placed Harrison-Anderson-Mick (HAM) Applicators for the Treatment of Retroperitoneal Sarcomas: A Novel Alternative to IORT and Adjuvant External Beam Radiation

G. Falk, G. Morris-Stiff, M. Walsh, K. Stephans, P. Escobar, S. Chalikonda.* *general surgery, cleveland clinic, Shaker Heights, OH.*

Background Surgical resection is the treatment of choice for retroperitoneal sarcomas, however recurrence is common, and is associated with poor outcomes. Evidence exists that adjuvant irradiation may improve local tumor control. We present a technique for local delivery of high-dose radiation to the tumor bed of resected retroperitoneal sarcomas via Harrison-Anderson-Mick (HAM) applicators placed intra-operatively. Material and Methods From May 2009 to July 2011 patients with surgically resectable retroperitoneal sarcomas deemed suitable for post-operative radiotherapy were included in the study. All patients underwent sarcoma resection and concurrent placement of a (HAM) radiation applicator into the tumor bed. Packs were utilized to isolate adjacent bowel from the irradiated area. (Figure 1) The abdomen was then closed and postoperative CT-guided brachytherapy performed. After completion of therapy, patients were brought back to the operating room for removal of the HAM applicators and associated packs. Results During the period covered by the study, 11 patients underwent concomitant sarcoma resection with HAM-guided radiotherapy. Seven patients received 9 Gy in 2 fractions whilst the remaining were prescribed 3 fractions of 7 Gy. The average dose at the prescription point (1cm from source at applicator centre) was 33.6 Gy for the 9 Gy group and 32.2 Gy for the patients receiving 7 Gy. There were no complications related to HAM catheter placement or removal. No patients in the series have experienced radiation related skin or bowel complications. Conclusion Perioperative brachytherapy delivered via intra-operatively placed HAM applicators at the time of retroperitoneal sarcoma resection allows accurate delivery of a higher total dose of radiation, while minimizing damage to the surrounding normal tissue. This also obviates the need for external beam radiation therapy and is a suitable alternative to IORT.

Figure 1



a-preoperative ct demonstrating retroperitoneal sarcoma
b. CT demonstrating resected sarcoma. Arrows indicated operative packs and HAM catheters in resection bed.

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Complications of Cemented Long-stem Hip Arthroplasties in Metastatic Bone Disease: Revisited

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Introduction: Literature supports the notion that cemented long-stem femoral arthroplasty is associated with increased intraoperative and perioperative risk. Specifically, embolic events may precipitate cardiopulmonary complications even death. It has been recently suggested that the use of cemented long–stem femoral arthroplasty in patients with metastatic bone disease is a safe procedure. To further support this idea, we retrospectively reviewed the results of an additional 44 long-stem cemented femoral arthoplasties employing methods to minimize intraoperative cement-related emboli. Methods: A retrospective chart review was performed of patients treated with long-stem cemented hip arthroplasty for impending or recognized pathologic fracture secondary to metastatic bone disease. The medical records of patients alive at the conclusion of the previous study were reviewed to see if complications developed since the initial investigation. An additional 42 patients were reviewed, the primary outcome measure being peri-operative complications. Specific variables include intra-operative cement associated desaturation, cement associated hypotension, sympathomimetic administration, post-operative hypotension, desaturation and death. The surgical procedure was standardized. Results:

In this new cohort of 42 patients and 44 arthroplasties, 18% had cement-associated hypotension, and sympathomimetics were administered to 45%. Prolonged intubation was required for 2 patients. There was one death that occurred during hospitalization. This patient had advanced metastatic disease and was found to have post-operative anemia, which was refractory to volume resuscitation. There were no cardiopulmonary events, no perioperative desatuation, and no perioperative deaths. Of those alive at the end of the previous study, no further records were available for 6, the remaining died from their disease. Conclusion: Having now reviewed the hospital records of a total of 69 patients who underwent a total of 73 cemented arthroplasties, our data suggests that with our technique, cemented long stem hip arthroplasty is a safe treatment option for those with metastatic bone disease.

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Extra-intestinal Tumor Location is a Poor Prognostic Factor for Primary Non-metastatic Gastrointestinal Stromal Tumors

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Background: Gastrointestinal stromal tumors(GISTs) are the most common mesenchymal neoplasm of the GI tract. Tumor size, tumor location, and mitotic index are established factors that risk stratify recurrence and survival. Extra-intestinal GISTs are infrequently observed and our objective was to determine the outcomes of patients with primary GISTs found outside the GI tract. Methods: The Surveillance Epidemiology and End Results registry was used to identify patients with GIST treated with surgery between 1996 and 2008. Patients were evaluated by standard clinical and pathological indices including: age, primary tumor location (extra-intestinal vs. GI tract), tumor size, tumor grade, and extent of disease. Overall survival differences between primary site groups were assessed by Kaplan-Meier method. Univariate and stepwise multivariate Cox proportional hazards analyses were performed. Results: Of the 2812 patients with surgically treated GIST, 2489 (88.5%) had a primary tumor location in the GI tract and 323 (11.5%) were located in extra-intestinal sites. Comparison of patients by primary tumor location demonstrated more locally advanced cancers with lymph node involvement (40.2% vs. 18.4%; p<.0001) and a higher occurrence of distant metastatic disease (22.3% vs. 16.6%; p<.0001) among the extra-intestinal GISTs. When comparing overall survival, patients with extra-intestinal GISTs had significantly worse 5 year survival (62% vs. 70%, respectively; p=0.002) than patients with primary tumors within the GI tract. Stepwise multivariate analysis showed that non-intestinal site was an independent predictor of poorer survival (HR 1.29, 95% CI [1.05-1.59], p=0.015). Conclusion: Our data indicates that extra-intestinal location for primary non-metastatic GIST is an independent poor prognostic factor, with worse overall survival, compared to GISTs located within the GI tract. Risk stratification for prognosis should account for these rare GIST locations.

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Prognostic Factors and Outcomes of Patients with Myxofibrosarcoma N.J. Look Hong,* G.P. Nielsen, F.J. Hornicek, K.A. Raskin, D. Springfield, S.S. Yoon, A.E. Rosenberg, Y.L. Chen, T.F. DeLaney, J. Szymonifka, J.T. Mullen. *Massachusetts General Hospital, Boston, MA.*

Background: Myxofibrosarcomas (MFS) are a historically heterogeneous group of soft tissue tumors which exhibit a propensity for local recurrence. The objectives of this study were to describe the clinicopathologic prognostic factors and outcomes of patients with MFS treated at a single institution and to define an optimal treatment approach. Methods: We retrospectively reviewed records of 69 consecutive patients with localized, pathologically-confirmed myxofibrosarcomas of the extremities or superficial trunk who underwent surgery at our institution from January 1995–November 2010. Clinicopathologic characteristics, treatment approaches and patient outcomes were reviewed and analyzed. Results: Sixty-nine patients were identified, of whom 38 (55%) were male. The median age was 62 years (range 19-94). Sixty-four (93%) patients presented with primary tumors, and 5 (7%) patients presented with locally recurrent tumors. Median tumor size was 6.0cm, and 16 (23%) and 44 (64%) patients had grade 2 and 3 tumors, respectively. Margins were microscopically positive in 14 (20%) patients and close (<1 mm) in 14 (20%) patients. Fifty (73%) patients received radiation therapy and 13 (23%) patients received chemotherapy. At a median follow-up of 30 months, there were 11 (16%) local, 2 (1%) nodal and 11 (16%) distant recurrences. The local, regional and distant 5-year recurrence free survival (RFS) rates were 72%, 96% and 82%, and the 5-year overall (OS) and disease-free survival (DSS) rates were 61% and 81%, respectively. Age (HR=1.76,p=0.002) and tumor size (HR=1.12,p=0.006) were statistically significant independent predictors of OS. Recurrent status (HR=8.94,p=0.007) and positive/close margin status (HR=2.73,p=0.041) predicted RFS. All 9 (13%) patients with grade 1 tumors were recurrence-free at 5 years. Three patients experienced multiple local recurrences, including 2 patients who required amputation. Conclusions: Myxofibrosarcomas exhibit a high propensity for local recurrence and should be aggressively resected for local control. Radiation therapy may contribute to improved local control, but further study of a larger population of patients is required.

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Complete Lymph Node Dissection for Stage III Soft Tissue Sarcoma Identifies Occult Disease J.L. Deneve,* J.S. Zager, A.P. Conley, K. Henna, M.M. Bui, D. Cheong, D. Reed, R. Lavey, D.G. Letson, R.J. Gonzalez. *Surgical Oncology, Moffitt Cancer Center, Tampa, FL.*

Introduction: The role of complete lymph node dissection (CLND) for soft tissue sarcoma (STS) with isolated regional lymph node (LN) metastasis is unclear. We review our CLND experience for STS metastatic to regional LNs. Methods: After IRB approval, our institutional database from 1998-2010 was reviewed to identify STS patients who underwent lymphadenectomy. Clinical characteristics were recorded and standard statistical analysis was performed. Results: Of 2127 STS patients in our registry, thirty-six patients (1.7%) were coded as having a LN procedure. Of these, 19 patients were excluded for bystander nodal excision upon resection of primary tumors. Formal CLND was performed in 17 pts (0.8%) for known regional disease. 15 patients (88%) underwent primary tumor R0 or R1 resection. Median age was 61 years, 53% were male. CLND was performed at time of primary tumor extirpation in 47% and for recurrence in 53%. Three patients (18%) had evidence of distant disease and underwent palliative CLND. A median of 15 LNs were excised, median size 3.9 cm. 47% had additional involved LNs identified pathologically (3.6±0.9) than was initially evident by pre-operative imaging or clinical exam (1.3±0.3, p=0.057). Postoperative complications were noted in 24%. Four patients (24%) developed extremity lymphedema. 9 patients (53%) received adjuvant radiation after CLND while 6 patients (35%) received adjuvant chemotherapy. Three patients (18%) recurred after after CLND, 1 regional and 2 distant. After a median follow up of 23 mos from diagnosis (range, 3-124), 47% were alive without disease, 24% alive with disease and 29% had died of disease-related causes. Median OS was 31 mos, median RFS was 16 mos and 5 year OS was 44% after diagnosis of the primary tumor. Median OS was 13 mos, median RFS was 9 mos and 5 year OS was 23% after CLND. Conclusion: CLND may benefit STS patients with isolated regional LN metastases in this highly select case series. While excision of only clinically evident nodal disease alone is advocated by some, formal CLND removes additional disease. Furthermore this can be accomplished with limited morbidity, and reasonable local control and overall survival.

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Surgical Resection of Retroperitoneal Sarcomas: Analysis of Factors Determining Outcome D. Shouhed,* F. Amersi, L. Marsh, C. Forscher, A.W. Silberman. *Surgery, Cedars-Sinai Medical Center, Los Angeles, CA.*

Introduction: Retroperitoneal (RP) and pelvic sarcomas (PS) are rare, malignant tumors characterized by high local recurrence rates, and poor survival. Aggressive surgical resection may improve local recurrence rates and disease-specific survival. The aim of our study was to determine predictors of survival and local recurrence in primary RP and pelvic sarcomas. Methods: We performed a retrospective analysis and identified 68 patients who underwent surgical resection of a primary RP and PS between 1985 and 2010. Age, gender, tumor location, size, grade, histology, vascular involvement, extent of surgical resection, and margins were used to create univariate and multivariate models for both survival and recurrence. Results: 68 patients (37% male and 63% female) with a mean age of 59 (range 25-84) underwent surgical resection for RP and PS . Median tumor size was 12.0 cm (range: 7.0 – 18.0 cm) with 75% being intermediate or high-grade. Incontinuity organ resections were performed in 43% of pts. Seven pts (10%) underwent vascular resection with graft placement. Overall survival at 5, 10, and 15 years was 89%, 55%, and 42%, respectively. In a multivariable model, factors that significantly affected overall sur-

vival were recurrent disease (p<0.001), age (p<0.003) and high/intermediate grade (p<0.001). Incontinuity organ resection, regardless of whether final pathology revealed metastatic disease, did not significantly affect overall survival (Hazard Ratio = 1.4, CI 0.8 - 2.9). Grade (low vs. intermediate/high; p<0.007) and margin status (p<0.05) were found to be the only variables that significantly affected overall recurrence. In continuity organ resection, regardless of final pathology, did not significantly affect recurrence (Hazard Ratio=1.075, CI 0.625 - 1.851). Over a 25 year follow-up, 37 patients (54%) died. Conclusion: Surgical resection of RS affords the best chance of survival. Incontinuity organ resection did not affect outcome on multivariate analysis; however, margin status did significantly affect recurrence, and could not be achieved without aggressive resection of incontinuity organs.

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Desmoplastic Small Round Cell Tumor (DSRCT): A Population-based Study from the Surveillance, Epidemiology, and End Results (SEER) Database S.L. Cooper,* K. Armeson, E. Garrett-Mayer, M. Hudspeth, J. Jenrette, R. Camp, C.J. Streck. *Medical University of South Carolina, Charleston, SC.*

Introduction: DSRCT is an uncommon and aggressive malignancy of children and young adults with limited information regarding presentation and management. A population-based database was evaluated to determine prognostic factors for this disease. Methods: A query of the SEER database (1991-2008) was performed for patients with a diagnosis of DSRCT. Incidence, demographics, prognostic variables, outcomes and treatment trends were analysed. Percent survival was calculated using Kaplan-Meier estimates with death from disease as the event. Cox proportional hazards regression was used to assess the effects of age, race, gender, year of diagnosis, primary site, tumor size, radiation, stage, and extent of surgery on survival. Results: There were 192 patients with median follow-up of 16 months. Median age was 26 years, 78% were male, 70% were Caucasian and 24% African American. Primary site was 26% pelvis/retroperitoneum, 49% abdomen/peritoneum, 17% other, and 9% unknown primary. Stage at presentation was 6% localized, 17% regional, 67% distant, and 10% unknown. Average primary tumor size was 12.4 cm. Overall survival (OS) and disease-specific survival (DSS) for all patients were 21 and 23 months, respectively. On multivariate analysis (N=83), tumor size (p=0.06), stage (p<0.01), and extent of surgery (p<0.01) were associated with DSS. Hazard ratio (HR) for distant disease vs. localized/regional = 3.2 (95% CI: 1.5-6.9). HR for complete excision vs. partial/none = 0.4 (95% CI: 0.2-0.7). On subset analysis, complete excision was associated with improved DSS in patients with localized/regional disease (p = 0.01) as well as in patients with distant disease (p<0.01). Radiation therapy was utilized in 26% of all patients. Conclusion: DSRCT is a rare malignancy which commonly presents with distant disease and has poor overall survival. Tumor size, extent of disease and surgical resection are important prognostic factors. Little evidence is available to guide adjuvant or neoadjuvant therapy in patients following resection as few patients presented with localized disease and no validated staging systems exists.

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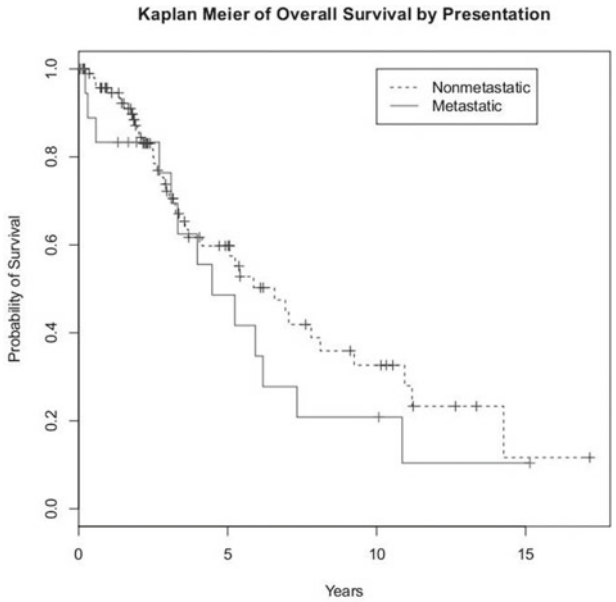
Single Institution Review of Outcomes in Retroperitoneal Soft Tissue Sarcomas A.A. Guzzetta,[1]* K. Ibrahim,[2] E.P. Pappou,[1] T. Fu,[1] J. Jeschke,[1] B.H. Edil,[1] E.A. Montgomery,[2] N. Ahuja.[1] *1. Surgery, Johns Hopkins University, Baltimore, MD; 2. Johns Hopkins University, Baltimore, MD.*

Introduction: Retroperitoneal soft tissue sarcomas (RSTS) are relatively rare entities and the only possibility for cure is complete resection. We now review our primary RSTS for factors relating to prognosis and recurrence. Methods: A retrospective chart review was performed of patients who received treatment for RSTS at our institution from 1984 to 2010. Kaplan-Meier survival analysis, log-rank test, and Cox-regression were used to correlate tumor presentation and survival. All available pathology slides were reexamined by a pathologist to confirm the diagnosis. Results: 169 patients were treated for their RSTS. Mean age at presentation was 56 years with 81 (48%) males. 39 patients (23%) had metastasis on presentation with most common sites being liver 14 (36%), lungs 8 (21%), or both 5 (13%). 149 (88%) patients underwent surgery with curative intent. Of these, 120 (76%) had a complete (R0/R1) resection, 19 (12%) had an R2 resection, and 10 (6%) had missing margin status. Major histologies seen were leiomyosarcomas (36%) and liposarcomas (31%). Mean tumor size was 15.7 cm and majority were high-grade (grades 2/3: 82%). Overall 5 year survival for all patients (n=169) was 45%. Overall 5-year survival for patients without metastasis undergoing R0/R1 resection was 60% and it was 49% for RSTS which presented with distant metastasis (p=0.30). On Cox regression analysis, margin status, presence of distance metastases and tumor size correlated with overall survival and recurrence (p<0.05 for all). Conclusion: Margin status continues to be of critical importance in RSTS patients. Curative resection with long-term survival is possible in patients with distant metastasis.



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Small Improvements in Survival Explained by Changes in Stage Distribution for Older Patients with Extremity Soft-tissue Sarcoma M. Hoven- Gondrie,[1]* E. Bastiaannet,[2] V. Ho,[3] B. Van Leeuwen,[1] G. Liefers,[2] A. Suurmeijer,[1] H. Hoekstra.[1] *1. UMCG, Groningen, Netherlands; 2. LUMC, Leiden, Netherlands; 3. CCCN, Utrecht, Netherlands.*

Introduction Soft-tissue Sarcomas are relatively rare tumors and account for 1% of all cancers in adults. About 40% of patients are 65 years and older and this proportion is expected to increase due to aging of the population. However, data concerning older patients with sarcoma are scarce. Aim of this study was to assess time trends in stage, treatment and survival for older patients with extremity soft-tissue sarcoma (ESTS). Methods All patients 65 years and older diagnosed between 1989 and 2008 were selected from the national cancer registry. Stage at diagnosis over time was assessed using a multivariable regression analysis. Treatment was divided in no treatment, only surgery, radiotherapy (RT) or chemotherapy (CT) and any form of combined therapy. Analyses were stratified for age categories and changes over time were tested with multivariable regression analysis. Finally, relative survival was used to study trends in survival over time. Results Overall, 1527 patients were included. Stage distribution over time changed with more low stage and less high stage sarcoma (p<0.001). The proportion of older patients receiving no treatment or only surgery increased with age and over time. Relative

Survival decreased with age, especially in the very old, showing a high excess mortality due to sarcoma. Over time, there was only a small improvement in survival (RER per year 0.98 (95%CI 0.96-1.00); p=0.02). However, changes in stage distribution explained this improvement (RER adjusted for stage 1.01 (95%CI0.99-1.03); p=0.4). Conclusion Today older patients are more often diagnosed with low stage ESTS which explained the small improvement in survival over time.

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Surgical Management of Retroperitoneal Sarcoma (RPS): A Single Institution Experience C.R. Rossi,[2] A. Varotto,[1] S. Pasquali,[1]* L.G. Campana,[2] A. Sommariva,[2] A. Vecchiato,[2] S. Mocellin,[1] P. Pilati,[1] D. Nitti.[1] *1. Dpt. of Oncological & Surgical Sciences, University of Padova, Padova, Italy; 2. Veneto Institute Of Oncology, Padova, Italy.*

Introduction: Resection of uninvolved adjacent viscera has been suggested for improving tumor local control after surgery in patients with RPS. This study sought to investigate local disease free survival (LDFS) and overall survival (OS) after potentially curative surgery performed by resecting adjacent organs when apparently involved by tumor, in patients with primary or recurrent RPS. Methods: Clinical records of patients with RPS treated with curative intent in our Department (1989-2010) were reviewed. The following clinical and pathological features were considered: gender, age, presentation (primary versus recurrent tumors), tumor size, RPS histotype, tumor grade, excision margins, and resection of adjacent organs. Adjacent viscera were resected only when apparently involved. Results: Eighty patients with RPS were treated, 42 (52%) had primary tumor, while the remaining 38 (48%) were resected for recurrent disease. R0 resection margin were achieved in 16 (20%) patients. RPS There were 42 liposarcomas (53&) and 17 leiomyosarcomas (22%). High grade tumors were detected in 29 patients (37%). Adjacent organs were apparently involved and thus resected in 48 cases (58%). Post-surgery morbidity rate was 16%. Median follow up was 39 months (range, 6-261). Five-years LDFS was 54% (95%CI, 40-66%). Patients with primary and recurrent disease had 81% and 22% 5-year LDFS rates, respectively (P<0.001). At multivariate analysis for LDFS, tumor presentation was the only independent prognostic factor (higher risk of local relapse for recurrent sarcomas, HR 6.65, 95%CI 2.03-21.8, P=0.002). Five-year OS was 42% (95%CI, 29-5%). At multivariate analysis for OS, resection margins were the only independent prognostic factor (R1 vs. R0 HR 3.75, 95%CI 1.28-10-94, P=0.016). Conclusions: Patients with primary RPS had greater LDFS than those with recurrent disease. Considering the potentially curative role of achieving a R0 resection after surgery, a more aggressive approach, such as that of multivisceral surgery, may be considered particularly in patients with recurrent RPS.

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One Stage Sacral Resection for Primary Sacral Tumours W.S. Gawad,* M.M. Khafagy, M.H. Gameil, I.H. Mourad, M.H. Negm. *Surgical Oncology, National cancer Institute, Cairo, Egypt.*

Background En bloc sacral resection with adequate margin provides a chance for cure for primary sacral tumours despite the complexity of the approach and the associated morbidity. Patients and methods Sixteen consecutive patients underwent sacral resection between 2003-2010. Chordoma was the most frequent tumour (7 patients),benign neurogenic tumours in 2 patients,malignant nerve sheath and chondrosarcoma in 3 patients for each and one patient with giant cell tumour. Subtotal sacral resection below S1 was conducted in 15 patients and one patient underwent total sacrectomy. Results Resection with negative margin (R0) was achieved in 6 patients (37%) and with microscopic margins (R1) in 10 patients (63%).Surgical mortality was nil, morbidity was evident in 56%.Six patients had wound gap,2 patients developed neurogenic bladder and one patient developed enteric fistula. Blood transfusion ranged from (0.4-6litres).Median hospital stay 22(7-65) days. The Median disease free survival for patients with chordoma was 62 months (Kaplan meier) Conclusion One stage sacrectomy for primary sacral tumours can be safely achieved with free margins with an acceptable morbidity and oncologic outcome.

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The Safety of Preoperative/Intraoperative Radiation Therapy for Retroperitoneal Sarcomas R. Sharma,[1] A. Miller,[3] K. May,[2] J.M. Kane.[1]* *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. Roswell Park Cancer Institute-Radiation Oncology, Buffalo, NY; 3. Roswell Park Cancer Institute-Biostatistics, Buffalo, NY.*

INTRODUCTION: Preoperative radiation therapy (preRT) is often used for high risk extremity sarcomas, but with increased postoperative wound healing issues. Its role in retroperitoneal sarcomas (RPS) is less clear, including potential toxicity to critical intra-abdominal structures. Our institutional preference has changed to favor preRT and selective intraoperative HDR brachytherapy (IOBT) for patients undergoing surgical resection of RPS. METHODS: Retrospective review of all RPS patients (primary and recurrent) presenting for surgical resection from 2002-2010. Tumor characteristics, patient demographics, operative details, postoperative complications, and outcome were analyzed. RESULTS: 37 patients were analyzed. Median age was 57 years and 65% were female. 18 patients (48.6%) received preRT followed by surgery (S) with a median dose of 50.4 Gy (range 45-54). 9 patients (24.3%) also had IOBT with Iridium 192 (median dose 12.5 Gy, range 7.5-15). There was no difference in primary/recurrent presentation between preRT+S vs. S alone (72%/18% vs. 74%/16%, p=0.72). However, in the preRT+S group, non-liposarcoma histology (50% vs. 21%, p=0.12), high grade tumors (56% vs. 22%, p=0.03), and left side (76% vs. 39%, p=0.02) were more common. For preRT+S vs. S alone, median number of organs resected (4.5 vs. 3, p=0.06) and microscopically negative final resection margins (65% vs. 61%, p=0.10) were similar, but median hospital stay was slightly longer (12 vs. 8.5 days, p=0.03). Major intra-abdominal postoperative complication rates were comparable in both groups (Table 1). At a median followup of 30 months (range 2-107), local recurrence (LR) and distant recurrence (DR) rates for preRT+S vs. S alone were 38% vs. 47% (p=0.64) and 15% vs. 12% (p=0.77), respectively. CONCLUSIONS: The addition of preRT to S for RPS appears to be safe and well tolerated. Despite higher risk features as compared to the S alone group, LR and DR rates were similar. Therefore, preRT+S may have a therapeutic role in high risk RPS patients.

Table 1.

Postoperative Complication	S alone	preRT+S	p value
GI fistula	0	1 (5.6%)	0.298
abdominal abscess	0	1 (5.6%)	0.298
wound infection	3 (15.8%)	3 (16.7%)	0.942
bowel obstruction	0	1 (5.6%)	0.298
sepsis	1 (5.3%)	3 (16.7%)	0.264
renal failure	0	1 (5.6%)	0.298
neuropathy	0	1 (5.6%)	0.298

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Does a Common Vascular Origin Confer Similar Prognosis to Malignant Tumors of the Liver? R.T. Groeschl,* S.G. Pappas, K.K. Christians, S. Tsai, E.J. Quebbeman, T.C. Gamblin, K.K. Turaga. *Medical College of Wisconsin, Milwaukee, WI.*

BACKGROUND: Unlike the ubiquitous hepatic hemangioma, malignant vascular tumors (MVT) of the liver are uncommon and poorly understood. We hypothesized that tumor histology is a predominant factor associated with survival in these tumors and describe features of these uncommon tumors. METHODS: Patients with malignant histopathologic diagnoses of hepatic angiosarcoma (AS), hemangioendothelioma (HE) and its epithelioid variant (EHE), or hemangiopericytoma (HP) were identified using the Surveillance, Epidemiology, and End Results (SEER) database (1973-2007). Standardized incidence rates were calculated based on the 2000 U.S. population. Overall survival (OS) was studied with

the Kaplan Meier method, and prognostic factors were studied with Cox regression modeling. RESULTS: We included 297 patients with MVT (207 AS, 28 HE, 56 EHE, 6 HP) with an annual standardized incidence of 3 per million. Patients with AS were likely to be older at diagnosis (median 63 yrs, p = 0.001) and less likely to be female (38%, p < 0.001, Table 1). All tumors demonstrated significant metastatic potential, although EHE and AS had the highest rate of regional or distant metastases (75% each, p = 0.05). Patients with AS had the shortest median OS (1 month [IQR 1-2]), however those undergoing surgery had improved survival (6 months [IQR 3-25]). Three patients with AS underwent a hepatic transplant and lived for 11, 21 and 91 months each. Patients with EHE had the overall longest median survival of 75 (30-183) months (p < 0.001). Surgical resection and transplant did not improve the overall survival of patients with EHE in multivariate models (p = 0.2, 0.9). CONCLUSIONS: Histology is an important factor in determining survival for patients with hepatic MVT. Patients with EHE have the longest OS even in the absence of surgical intervention, whereas patients with AS have shorter survival but appear to benefit from surgery. Our data is limited by the lack of tumor and patient characteristics available in the dataset.

Demographics and Outcomes of Vascular Liver Tumors, by Histologic Type

	AS	HE	EHE	HP	Total	p-value
# of Patients	207	28	56	6	297	
Median Age at Diagnosis (IQR)	63(53-74)	53 (46-67)	50 (39-65)	50 (43-53)	59 (48-72)	<0.001
# of Females (%)	80 (39)	19 (68)	41 (73)	3 (50)	143 (48)	<0.001
SEER Stage (%) (n=251)						
Local	42 (25)	10 (42)	13 (25)	4 (67)	69 (27)	0.05
Metastatic	127 (75)	14 (58)	39 (75)	2 (33)	182 (73)	
Tumor size, cm (IQR) (n=39)	10 (6.1-12)	3.7 (2.5-5.0)	3.4 (2.3-55)	10.8 (-)	7.7 (3.8-10.8)	0.001
Surgery (%) (n=191)						
No Surgery	107 (78)	7 (54)	31 (70)	2 (40)	147 (74)	0.04
Local Ablation	1 (1)	0	1 (2)	0	2 (1)	
Segmental Resection	18 (13)	4 (31)	5 (11)	1 (20)	28 (14)	
Lobectomy/Extended Resection	3 (2)	0	2 (5)	0	5 (2)	
Transplant	3 (2)	0	5 (11)	1 (20)	9 (4)	
Median OS, mo (95% CI)	1 (1-2)	4 (1-16)	75 (30-183)	12	2 (2-3)	
1-year OS: Observation	7	28	67	50	22	
1-year OS: Surgical Resection	28.5	25	57	100	38	
1-year OS: Transplant	67	-	80	100	76	

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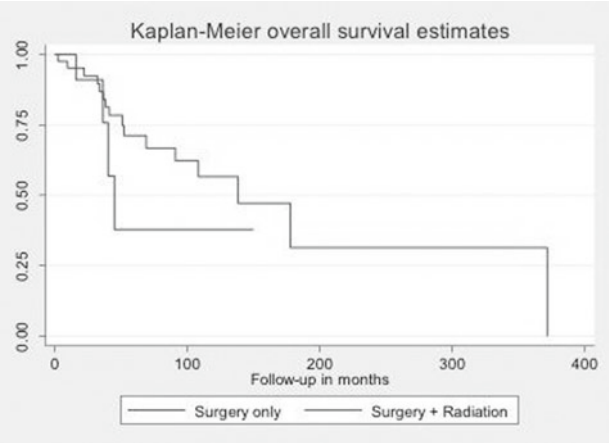
Is There a Role for Radiotherapy in the Management of Retroperitoneal Sarcoma: A Single Institutional Experience S. Zani,[1]* A.W. Maiga,[1] K. Papalezova,[2] S.S. Stinnett,[1] B. Czito,[1] D.S. Tyler,[1] D. Blazer, III.[1] *1. Duke University Medical Center, Durham, NC; 2. Montefiore Medical Center, Ney York, NY.*

Introduction: Retroperitoneal sarcomas are rare neoplasms. Complete tumor resection continues to be the mainstay of modern therapy. However, despite aggressive surgical resection strategies, locoregional recurrence is common. Adjunctive therapies such as external beam radiotherapy and intraoperative radiation therapy have shown promising results though data are limited. The objective of this study was to evaluate outcomes in patients undergoing surgery for retroperitoneal sarcoma in a single institution and then to compare outcomes in those patients undergoing surgery alone versus surgery and radiation therapy. Materials and Methods: Under IRB approval, 52 patients undergoing surgery for retroperitoneal sarcoma were identified during the period 1990-2010. Eleven patients underwent surgery alone while 41 patients underwent either external beam and/or intraoperative radiation therapy in addition to surgical resection. Prognostic factors such as age, gender, completeness of resection (R0, R1, or R2), pathologic grade, and tumor size were evaluated. Kaplan-Meier survival curves were generated and compared. Results: Median follow-up was 45.9 months for all patients. Three-year and 5-year overall survival for all patients from initial diagnosis was 86.1% and 66.7%, respectively. Median disease-free survival (DFS) for the 11 patients who underwent surgery alone was 21.7 months versus 31.8 months for the radiation plus surgery group (n=26) (p=0.7553). Overall median survival (MS) for the surgery alone group was 36.2 months whereas the radiation plus surgery group demonstrated MS of 51.9 months (p=0.1336). Conclusion: Data are limited regarding the benefits of radiation therapy in the management of surgically resectable retroperitoneal sarcoma. Though our numbers are small, these results demonstrate a trend toward improved median overall survival for patients treated with surgical resection and radiotherapy and make a compelling case for continued investigation into the role of adjunctive radiation therapy strategies in the surgical management of this difficult disease.



Overall survival estimates comparing surgery alone to surgery with radiation therapy (p=0.1336).

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Phase 1 Trial of Gene Mediated Cytotoxic Immunotherapy Combined with Resection for Pancreatic Adenocarcinoma L.A. Shirley,[1]* C. Marsh,[2] J. Walker,[1] W. Coyle,[2] S. Tahiri,[1] V.M. Chung,[3] M. Bloomston.[1] *1. The Ohio State University Medical Center, Columbus, OH; 2. Scripps Green Hospital, La Jolla, CA; 3. City of Hope National Medical Center, Duarte, CA.*

Background: While surgical resection of pancreatic adenocarcinoma provides the only chance of cure, long-term survival is still poor. Immunotherapy approaches may improve outcomes. Gene Mediated Cytotoxic Immunotherapy (GMCI) generates a systemic anti-tumor vaccine effect through intra-tumoral delivery of an adenoviral vector expressing the HSV-thymidine kinase gene (AdV-tk) followed by anti-herpetic prodrug administration. This is the first application of GMCI in pancreatic cancer. Methods: This study evaluated 4 dose levels of AdV-tk ($3x10^{10}$ to $1x10^{12}$ vector particles) injected into pancreatic tumors via EUS 2 weeks before resection. Patients then underwent attempt at resection. If resection was undertaken, AdV-tk was injected into the resection bed. If resection was not possible, AdV-tk was injected into the primary tumor. The prodrug, Valacyclovir, was given for 14 days after each injection. Post-operative therapy was not protocol-driven. Results: The study accrued 14 patients with 12 completing therapy: 3 at each of the 4 planned dose levels. One patient died of an unrelated myocardial infarction 2 days after initial injection and one patient dropped out mid-treatment after metastases were found at surgery. Median age was 67 years (range 40-81). Of 12 patients explored, 4 were not resected due to distant metastases (N=3) or locally advanced disease (N=1). Three patients had Grade 3 possibly-related adverse events: 2 abdominal pain and one dehydration with renal insufficiency. There were no dose limiting toxicities and no grade 4 clinical adverse events. Grade 3-4 laboratory abnormalities were AST/ALT, bilirubin, alkaline phosphatase and lipase, all in patients with obstructive jaundice. Post-operative complications included 2 patients who developed abscesses requiring drainage. Six of 12 patients are alive 5-34 months after start of treatment including 5 resected patients and one unresected. Conclusions: AdV-tk can be safely injected into potentially resectable pancreatic tumors prior to planned resection. Early results are encouraging and justify further evaluation in a Phase 2 study.

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Phase II Trial of Fixed-dose Rate Gemcitabine, Bevacizumab, and Concurrent 30 Gy Radiotherapy as Preoperative Treatment for Potentially Resectable Pancreatic Adenocarcinoma G. Van Buren,[1]* R.K. Ramanathan,[2] A. Krasinskas,[3] R. Smith,[4] G. Abood,[1] Y. Shuai,[5] D.P. Potter,[5] N. Bahary,[6] B.C. Lembersky,[6] A.H. Zureikat,[1] H.J. Zeh,[1] D.L. Bartlett,[1] A.J. Moser.[1] *1. Surgical Oncology, University of Pittsburgh, Pittsburgh, PA; 2. Translational Genomics Research Institute, Scottsdale, AZ; 3. University of Pittsburgh- Pathology, Pittsburgh, PA; 4. University of Pittsburgh- Radiation Oncology, Pittsburgh, PA; 5. University of Pittsburgh- Biostatistics, Pittsburgh, PA; 6. University of Pittsburgh- Medical Oncology, Pittsburgh, PA.*

Introduction: Effective multimodality treatment for localized pancreatic cancer is elusive. We hypothesized that preoperative fixed-dose rate(FDR) gemcitabine(GEM) combined with short-course radiotherapy(RT) and the angiogenesis inhibitor bevacizumab(BEV) would improve margin negative surgical outcomes and complete pathological response rates. Methods: Multi-site phase II trial evaluating all potentially-resectable pancreatic adenocarcinoma without major arterial involvement or portal venous occlusion. Dual primary endpoints included complete pathological response and margin negative resection rates of 10% and 80%. Subjects received FDR GEM on days 1, 15, and 29 combined with BEV(10 mg/kg IV), followed on day 43 by BEV and concurrent 30 Gy RT (3 Gy/fraction) over 10 days. After restaging, subjects underwent laparoscopy and possible resection after day 85. Stopping criteria required continuous monitoring of serious wound complications. Results: 58 subjects enrolled, of which 29 (50%) had suspected venous involvement. 57 completed treatment without dose-limiting toxicity or delays in surgery. Two grade 4 (3.4%) and 17 grade 3 toxicities (28.8%) occurred. Four patients progressed before surgery. 54 subjects underwent laparoscopy; ten had unexpected carcinomatosis, and one was unresectable. 43 subjects were resected (74%; 33 pancreaticoduodenectomy, 8 distal pancreatectomy, 1 total pancreatectomy, 1 Appleby); 19 (44%) required portal vein resection. Margin negative outcome was achieved in 38 (88%, 95% CI: 75%-96%) with one complete pathological response (2.3%; 95% CI: 0.1%- 12%) and seven (6 grade 3; 1 grade 4) wound complications (13%). Median overall survival (OS) was 16.3 months (95% CI: 13.9 -22.1) and 21.3 months (95% CI: 15.0-32.9) after resection. Median progression-free survival (PFS) was 5.7 months (95% CI: 3.9-9.1) and 9.9 months (95% CI: 5.7 to 14.1) after resection, with 7 local and 21 distant recurrences. Conclusion: Combination therapy was well-tolerated and was within statistical design parameters for the primary endpoints despite a significant proportion of borderline tumors.

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A RAND/UCLA Appropriateness Study of the Management of Familial Gastric Cancer M. Dixon,[1]* R. Seevaratnam,[1] D. Wirtzfeld,[2] R. McLeod,[1] L. Helyer,[3] C. Law,[1] C. Swallow,[1] L. Paszat,[4] J. Tinmouth,[5] R. Cardoso,[1] A. Mahar,[6] N. Coburn.[1] *1. Department of Surgery, University of Toronto, Toronto, ON, Canada; 2. Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; 3. Department of Surgery, Dalhousie University, Halifax, NS, Canada; 4. Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada; 5. Department of Gastroenterology, University of Toronto, Toronto, ON, Canada; 6. Department of Community Health and Epidemiology, Queens University, Kingston, ON, Canada.*

Background: Hereditary diffuse gastric cancer (HDGC) makes up 0.1-0.3% of all gastric cancers. Management of patients with HDGC is inconsistent and there is disagreement regarding management. Methods: A multi-disciplinary expert panel of 16 physicians from 6 countries scored 47 scenarios using the RAND/UCLA Appropriateness Methodology. Appropriateness was scored from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores (AS) from 1-3 were considered inappropriate, 4-6 uncertain, and 7-9, appropriate. Agreement was reached when 11 of 16 panelists scored the statement similarly. If a statement was agreed to be appropriate, it was given a necessity score (NS) in the same manner. AS and NS are reported if agreement was met. Results: Gastric cancer (GC) patients with a family history of diffuse gastric cancer (DGC), lobular breast cancer or multiple family members with GC should be referred for genetics assessment and multidisciplinary decision-making (AS 8.0). It is appropriate for patients with DGC to have CDH1 mutation testing in a family with: (1) two or more cases of GC, with at least one case of DGC diagnosed before the age of 50 (AS 8.0); (2) three or more cases of GC diagnosed at any age, one or more of which is DGC (AS 8.0); (3) a patient diagnosed with DGC and lobular breast cancer (AS 8.0); or (4) a patient diagnosed with DGC under the age of 35 (AS 7.0, NS 5.0). A prophylactic total gastrectomy should be offered to CDH1 mutation carriers 20 years or older (AS 7.0). Conclusions: The Gastric Cancer Processes of Care panelists have outlined high risk patients in whom CDH1 mutation status should be determined, and cases in which a prophylactic gastrectomy is appropriate.

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S-1 Combined with Oxaliplatin as Preoperative Chemotherapy followed by Surgery Shows Better Surgical Outcomes Compared with Surgery Alone for Advanced Gastric Cancer Patients T. Li,* L. Chen. *Chinese PLA General Hospital, Beijing, China.*

Background The only proven curative treatment for advanced gastric cancer is gastrectomy with D2 lymphadenectomy and microscopic disease (R0 resection).Some patients could benefit from preoperative chemotherapy by tumor downstaging. This study was conducted to evaluate the efficacy of S-1 combine with oxaliplatin (SOX regimen) as preoperative chemotherapy and compare surgical outcomes with surgery alone for advanced gastric cancer patients. Methods Stage III gastric cancer patients were enrolled in according to American Joint Committee on Cancer (AJCC, 7th ed.) TNM Staging and randomly assigned to preoperative SOX chemotherapy group and surgery alone. SOX regimen was consisted of S-1 80mg/m2/d p.o. on days 1-14 and oxaliplation 130mg/m2 i.v. on day 1, repeated every 21 days. All patients underwent surgical resection. Surgical outcomes and pathological results were compared.5-fluorouracil metabolic enzymes were analyzed by RT-PCR in fresh tissue for preoperative chemotherapy patients. Results From December 2009 to October 2010, 69 patients with stage III gastric cancer were enrolled in this study. 35 patients underwent two to four cycles of preoperative SOX chemotherapy. Tumor response was 68.5% and tumor control rate was 94.2%. 28 patients (80%) underwent D2 surgery and 30 patients (85.7%) performed R0 resection, significantly higher than surgery alone (P=0.041, P=0.040, respectively).Diffuse type gastric cancer patients had better pathology tumor response than intestinal type (P=0.041).Orotate phosphorybosyl transferase (OPRT) were found higher expression for pathological complete and partial response patients when compared with the others. Conclusion Patients after preoperative SOX chemotherapy showed better radical surgical outcomes than surgery alone, indicating the potential to be the first-line chemotherapy regimen for advanced gastric cancer patients. OPRT maybe an important biomarker to predict S-1 chemotherapy sensitivity.

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Establishing a HIPEC Program: What is the Financial Impact? C.X. Cruz Pico, G.A. Falk,* R. Walsh, P. Escobar, C. Michener, A. Thompson, S. Chalikonda. *Cleveland Clinic Foundation, Cleveland, OH.*

Background: Cytoreductive Surgery (CRS) and Hyperthermic Chemotherapy (HIPEC) are therapeutic modalitied used to treat selected patients with peritoneal carcinomatosis from several primary cancers. These treatments have been implemented successfully in tertiary care centers with high numbers of referrals. Materials: We present the first 39 patients undergoing CRS and HIPEC for intraperitoneal malignancies at our institution which follows the clinic model of healthcare, and analyze the financial implications of starting a new HIPEC program. Data were analysed from a prospective database of patients undergoing CRS and HIPEC from 1/1/2009 to 12/31/2010, and included demographics, net revenue and costs. Technical cost was broken down by resource utilization areas of anesthesia, imaging, nursing, pathology, pharmacy, surgical services, hospital stay. The contribution margin and net income was then calculated. Results:39 patients underwent CRS and HIPEC over the study period. Male to female ratio was 1:3, median age 53.2 yrs (range 28-76 yrs). Malignancies treated were primary peritoneal mesothelioma(n=4), gastric(3), ovarian(7), appendiceal(9), pseudomyxoma peritonei(8), colonic(8), cervical(1), gallbladder(1), urothelial(1) and duodenal(1). The median Peritoneal Cancer Index (PCI) was 9.4 (range 0-39) and an R0 resection was achieved in 32 patients. The total revenue generated was $4,025,967 with a contribution margin of $2,631,940. Total costs were $2,289,069 yielding net income of $1,736,897 (average $44,536 per patient). The majority of costs were attributable to surgical serv-

ices (40.6%), nursing (27.4%), pathology and laboratory (10.4%) and pharmacy (9.2%). Conclusion: We provide an estimate of the costs involved in implementing a successful CRS and HIPEC centre which provides surgical care for patients with intraperitoneal malignancies requiring specialized oncologic management whilst being a financially viable service capable of high revenue generation.

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A Multimodality Approach for Palliation of Symptomatic Malignant Dysphagia N.M. Rueth,[1]* D. Shaw,[1] J. D'Cunha,[1] C. Cho,[2] M.A. Maddaus,[1] R. Andrade.[1] *1. University of Minnesota Department of Surgery, Minneapolis, MN; 2. University of Minnesota Department of Therapeutic Oncology, Minneapolis, MN.*

Introduction: Dysphagia from advanced thoracic malignancies has a devastating impact on quality of life. While esophgael stents provide immediate palliation of malignant dysphagia, radiation therapy (XRT) is a superior longer-term option. We review the outcomes of combined esophageal stenting and XRT for patients with dysphagia from advanced thoracic malignancies. Methods: We retrospectively reviewed patients with esophageal stents placed for palliation of malignant dysphagia from esophageal stricture (ES), esophageal compression (EC), or malignant tracheoesophageal fistula (TEF). We excluded patients with radiation-induced TEF in the absence of tumor. We analyzed and compared outcomes between patients with no XRT, pre-stent XRT, and post-stent XRT. Results: We placed stents in 45 patients for: ES from esophageal cancer (n=30;66.7%), malignant TEF (n=8;17.7%), or EC from airway, mediastinal, or metastatic malignancies (n=7;15.6%). Twenty-five patients had XRT: pre-stent XRT (n=16;35.6%), post-stent XRT (n=8;17.8%), or both (n=1;2.2%). Twenty patients had no XRT. Median follow up was 30 days. Complications requiring stent revision were similar with or without XRT. Subjective symptom relief was achieved in 68.9% of all patients, with no differences noted between groups (p=0.99). Our 30-day mortality was 15.6%. Patients with post-stent XRT had a median survival of 98 days and patients without had a median survival of 38 days. Conclusion: Esophageal stent placement in combination with XRT is an acceptable multimodality approach for the palliation of dysphagia from advanced thoracic malignancies in select patients. These findings should encourage the initiation of multidisciplinary algorithms for early stent placement and combined XRT to maximize symptom palliation.

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Margin Distance is not an Independent Predictor of Survival after R0 Resection for Pancreatic Adenocarcinoma G. Van Buren,[1]* H.J. Zeh,[1] A. Krasinskas,[2] W.E. Gooding,[3] J. Steve,[1] K.K. Lee,[1] D. Magge,[1] M. Daouadi,[1] D.L. Bartlett,[1] A.J. Moser,[1] A.H. Zureikat.[1] *1. Surgical Oncology, University of Pittsburgh, Pittsburgh, PA; 2. University of Pittsburgh- Pathology, Pittsburgh, PA; 3. University of Pittsburgh- Biostatistics, Pittsburgh, PA.*

Background: Microscopic tumor at the surgical margin is a predictor of recurrence and poor survival for pancreatic ductal adenocarcinoma (PDA). However, the impact of distance between the surgical margin and microscopic tumor on survival remains controversial. We hypothesized that margin distance (MD) would correlate with disease free survival (DFS) and overall survival (OS) in R0 resected PDA. Methods: Retrospective analysis of 191 resections for PDA. Margin distance was measured (0-1, 1-2, 2-4, 4-10, and > 10 mm) and categorized by location. Parameters including age, gender, BMI, TNM, AJCC stage, lymph node (LN) ratio, vascular and perineural invasion, vein resection, and adjuvant therapy were analyzed. Primary endpoints were DFS and disease specific OS. Univariate analysis was used to estimate factors associated with outcomes. The log rank test was applied to selected group comparisons. Results: 149 (78%) R0 outcomes were analyzed. 118 (79%) patients received adjuvant chemotherapy, 31 of whom also received XRT. Univariate analysis demonstrated reduced DFS (HR = 1.65, 95% CI = 1.13 – 2.48, p = .009) and OS (HR = 1.52 95% CI =.98 – 2.35, p = .059) among patients with margins ≤ 2mm compared to margins > 2mm. In addition LN status, LN ratio, tumor size, AJCC stage, vascular invasion, perineural invasion and adjuvant chemotherapy were found to influence OS on univariate analysis. Adjuvant XRT had no measurable effect on DFS or OS. Following adjustment for covariates in a multivariate model, margin distance >2mm did not correlate with DFS (HR = 1.14, 95%CI = .73 – 1.78, p = .57) or OS (HR = 1.13 95% CI = .69 – 1.85, p = .63), whereas adjuvant chemotherapy and presence of vascular invasion significantly affected OS (P=0.0006 and P=0.008 respectively). The retroperitoneal margin was the margin most commonly in close proximity to tumor (43% of Whipple), although there was no correlation between the closest margin and DFS (p=0.94) or OS (p=0.94). Conclusion: Margin distance is not an independent predictor of DFS or OS after R0 resection for PDA. Irrespective of margin distance, adjuvant chemotherapy, but not XRT, was associated with improved OS.

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The Incidence and Preoperative Detection of Nodal Metastases in Resected Pancreatic Neuroendocrine Tumors J.M. Lindberg,[1]* D.M. Walters,[1] S.B. Edward,[2] A.B. Reid,[1] T.W. Bauer.[1] *1. University of Virginia - Department of Surgery, Charlottesville, VA; 2. University of Virginia - Department of Pathology, Charlottesville, VA.*

Introduction: Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of rare malignancies in which surgical resection remains the only curative therapy. The optimal surgical approach (enucleation vs. pancreatectomy) is controversial. The aims of this study were to determine the 1) incidence, 2) predictors, and 3) preoperative detection of lymph node (LN) metastases in resected pNETs in order to help guide surgical management. **Methods**: A retrospective review of prospectively collected data was performed for all patients with pancreatic neuroendocrine tumors who underwent surgical resection at the University of Virginia between 1991 and 2010. The electronic medical record, radiology reports and pathology reports were used to identify patient demographics, surgical procedure, tumor functional status, type, size, location, and LN status. **Results**: In all, 76 patients were identified. Most tumors were non-functioning (71%) with insulinomas (13%) and gastrinomas (5%) representing the largest groups of functioning pNETs. Nineteen tumors (25%) were found to have LN metastases at the time of resection. LN-positive tumors were significantly larger than LN-negative tumors (4.0 ± 0.4 cm vs. 2.8 ± 0.2 cm, p=0.01). Five (11%) of 46 tumors ≤ 3 cm and one (14%) of 7 tumors ≤ 1 cm had LN metastases. There were no significant relationships between LN status and either tumor type or location (head/uncinate vs. body/tail). Of the patients with LN-positive tumors, preoperative CT or MRI detected the LN metastases in only 19 percent. **Conclusion**: Twenty-five percent of pNETs are associated with LN metastasis. The only predictor of LN metastasis was tumor size, but even smaller tumors were associated with LN metastasis. The sensitivity of preoperative CT and MRI is quite poor in detecting LN metastasis. Thus, formal resection with lymphadenectomy should be considered the standard of care for pNETs.

	Node Positive	Node Negative	Total	*P*-value
Tumor Size (cm)*	4.0 ± 0.4	2.8 ± 0.2	3.1 ± 0.2	0.01
Tumor type:				
NF**	13	41	54	
Insulinoma	0	10	10	
Gastrinoma	3	1	4	
Glucagonoma	1	1	2	0.11
ACTH secreting	0	2	2	
Pheo	2	0	2	
Other***	0	2	2	
Tumor Location:				
Head/Uncinate	6	19	25	1.0
Body/Tail	12	38	50	

*Presented as mean +/- standard error
**Non-functioning tumors
***1 Pancreatic polypeptide secreting tumor, 1 PTH-like secreting tumor

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An Assessment of Feeding Jejunostomy Tube Placement at the Time of Resection for Gastric Adenocarcinoma S.H. Patel, D.A. Kooby, C.A. Staley, S.K. Maithel.* *Emory University, Division of Surgical Oncology, Atlanta, GA.*

Introduction Feeding jejunostomy tubes (J-tube) are often placed during gastrectomy for cancer to decrease malnutrition and morbidity, and promote delivery of adjuvant therapy. We hypothesized that J-tubes actually are associated with increased complications and do not improve nutritional status nor increase rates of adjuvant therapy. Methods: 132 patients were identified from a prospectively maintained database that underwent

gastric resection for gastric adenocarcinoma between 1/00-3/11 at one institution. Pre- and postoperative nutritional status and relevant intraoperative and postoperative parameters were examined. Results: Median age was 64 years (range 23-85). Forty-six (35%) underwent a total and 86 (65%) a subtotal gastrectomy. J-tubes were placed in 66 (50%) patients, half (n=34) of whom underwent a subtotal and half (n=32) a total gastrectomy. Preoperative nutritional status was similar between J-tube and no J-tube groups as measured by serum albumin (3.5 vs 3.4 g/dL) and BMI (26 vs 23). Tumor grade, T, N, and overall stage were similar between groups. J-tube placement was associated with increased postop complications (59% versus 41%, p=0.04) and infectious complications (36% versus 17%, p=0.01), of which majority were surgical site infections. J-tubes were associated with prolonged length of stay (13 vs 11 days; p=0.05). There was no difference in postoperative nutritional status as measured by 30, 60, and 90-day albumin levels and the rate of receiving adjuvant therapy was similar between groups (J-tube: 53%, no J-tube: 47%, p=0.48). Multivariate analyses revealed J-tubes to be associated with increased postop complications when accounting for tumor stage and operative difficulty and extent (Table). Subset analysis revealed J-tubes to have less associated morbidity after total gastrectomy. Conclusion: J-tube placement after gastrectomy for gastric cancer is associated with increased postoperative complications with no demonstrable advantage in nutritional status or adjuvant therapy. J-tubes should not be placed routinely after subtotal gastrectomy for gastric cancer, but may be selectively indicated in patients undergoing total gastrectomy.

Multivariate Regression Analysis for Increased Postoperative Complications

Variable	Odds-Ratio	95% CI	P-value
Age	1.03	0.99-1.07	0.18
ASA	1.59	0.46-5.45	0.46
Total Gastrectomy	0.72	0.21-2.45	0.59
EBL	1.00	0.99-1.01	0.68
T-Stage	1.06	0.62-1.79	0.84
N-Stage	1.43	0.87-2.34	0.16
J-Tube Placement	4.79	1.30-17.66	0.02

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Intraductal Papillary Mucinous Neoplasm (IPMN): MiRNA Molecular Profiling of Individuals at High Risk for Malignancy

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Introduction: IPMN represent a spectrum of tumors ranging from low grade dysplastic tumors to invasive cancer. Identification of malignant IPMN is important, as it would allow for true selection of patients most likely to benefit from surgery. We evaluated whether miRNAs are differentially expressed between low grade and malignant IPMN. Methods: All IPMN resected between 1995-2011 were reviewed by two GI pathologists. Forty five pathologically confirmed IPMN specimens were included and grouped into low risk (low/moderate grade dysplasia,, n=15) and high risk (high grade dysplasia, n=10; carcinoma, n=10; or low grade dysplasia micro-dissected from malignant IPMN, n=10) categories. 846 human miRNAs were profiled and cancer related differentially expressed miRNAs were validated using quantitative RT-PCR. Results: Hierarchical clustering demonstrated grouping of two main IPMN sub-groups: low grade versus high grade IPMN and carcinoma. We found that 24 miRNAs were differentially expressed (14 upregulated, 10 downregulated) in high grade IPMN and carcinoma compared to low grade IPMN ($p<0.05$). The expression of representing cancer related miRNAs (miR-21, miR-155, and miR-217) significantly differ between clusters (2 fold increase/decrease; $p<0.05$) and these were validated using quantitative RT-PCR showing that the expression of these specific miRNAs is associated with IPMN tumour aggressiveness. Interestingly, miR-155 expression level (in addition to other cancer associated miRNAs) and IPMN grade were directly proportional. Moreover, low grade IPMN samples that were dissected from tumors harboring remote carcinoma significantly differ from low grade IPMN and were also clustered in the high risk category. Conclusions: MiRNA expression patterns of low grade IPMN are different from malignant IPMN. Moreover, it demonstrates that cancer related miRNAs, i.e. miRNA-155, are specifically expressed in direct proportion to IPMN aggressiveness. This association indicates their biological relevance and highlights their potential for development as clinically significant biomarkers to better stratify high risk IPMN patients to surgery.

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Operability Classifications Predict Outcome of Patients with Anatomically Resectable Pancreatic Adenocarcinoma Treated with Neoadjuvant Therapy

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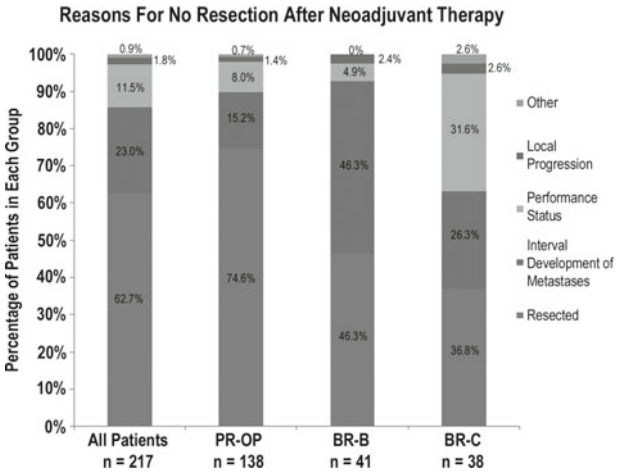
Background: We previously introduced a novel classification system for assessing "operability" in patients with localized pancreatic adenocarcinoma (PDAC) that integrates cancer biology, patient physiology, and tumor anatomy. We sought to analyze resection rates, reasons for no resection, and outcomes after neoadjuvant therapy (NT) of patients with both resectable anatomy and either "operable" or "borderline" biology/physiology. Methods: We evaluated consecutive patients (2002-2007) with radiographically resectable cancers treated with NT prior to potential resection. Borderline resectable anatomy (BR-A) was excluded. We compared clinical factors and outcomes of 217 patients classified by established criteria as "potentially resectable-operable" (PR-OP, no evidence of extrapancreatic disease, performance status [PS] ≤1); "borderline resectable-B" (BR-B, findings suspicious for extrapancreatic disease); or "borderline resectable-C" (BR-C, severe but reversible comorbidities or marginal PS ≥2). Results: 138 PR-OP, 41 BR-B, and 38 BR-C patients began NT. 62.7% of all patients underwent subsequent pancreatectomy. Resection rates after NT for PR-OP, BR-B and BR-C were 74.6%, 46.3%, and 36.8%, respectively ($p<0.001$). Metastases were detected during NT in 23.0% of all patients and were the most common contraindication to resection in PR-OP (15.2%) and BR-B (46.3%) patients. PS rarely precluded surgery except in BR-C patients (31.6%). Factors independently predicting not utilizing surgery after NT were older age, poor PS, new pain medications, and complications on NT ($p<0.05$). Median OS of all patients was 20.9 (95% CI, 17.1-27.1) mo. Resected and unresected BR-B and BR-C patients had OS similar to that of PR-OP patients (resected medians 33.0, 39.8, 36.0 mo, respectively; unresected medians, 10.1, 12.6, 12.9 mo; $p<0.001$). Conclusions: Our operability classification system describes discrete clinical subgroups among PDAC patients with similar, resectable tumor anatomy but vastly heterogeneous physiology and cancer biology. It can be used with NT to predict outcomes, individualize treatment, and optimize survival rates.



Resection was performed following neoadjuvant therapy in 74.6%, 46.3%, and 36.8% of PR-OP, BR-B, and BR-C patients, respectively. The interval manifestation of metastases was common in all groups, especially in BR-B and BR-C patients.

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Evaluation of Combination Treatment Benefits of nab-Paclitaxel in Experimental Pancreatic Cancer N. Awasthi,* K.T. Ostapoff, C. Zhang, M.A. Schwarz, R.E. Schwarz. *Surgery, University of Texas Southwestern Medical Center, DALLAS, TX.*

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human cancers and is characterized by early tissue invasion, metastasis and high resistance to systemic therapies. Gemcitabine, a standard cytotoxic therapy for pancreatic cancer, has shown limited clinical benefits. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel, Abraxane), an approved treatment for breast cancer, has shown efficacy as mono- and combination therapy in multiple tumor types including pancreatic, lung and ovarian cancer. We evaluated combination treatment benefits of nab-paclitaxel with gemcitabine in experimental pancreatic cancer. In vitro cell proliferation was evaluated by WST-1 assay in human PDAC cells. Animal survival studies were performed in AsPC-1 murine xenografts. Nab-paclitaxel inhibited in vitro proliferation of PDAC cell lines with IC50 levels of 7.6 μM, 208 nM, 519 nM and 526 nM for AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells. Nab-paclitaxel combination with gemcitabine had significant additive effect on inhibition of PDAC cell proliferation; 72-hour incubation demonstrated that nab-paclitaxel addition caused a 2.5, 2.5, 8.9 and 2.2-fold decrease in IC50 of gemcitabine in AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells, respectively. In an intraperitoneal murine xenograft model, 2-week therapy demonstrated that compared to controls (median survival: 23 days), animal survival increased after gemcitabine (27 days, p=0.05) and nab-paclitaxel monotherapy (35 days, p=0.0005). In a separate 3-week therapy experiment, animal survival was significantly longer in the nab-paclitaxel treated group (41 days, p<0.002 versus control and Gem) compared with gemcitabine (32 days, p=0.005 versus control), docetaxel (32 days, p=0.005) and controls (20 days). Animal survival in nab-paclitaxel / gemcitabine and docetaxel / gemcitabine sequential treatment group was 43 and 40 days, respectively. Nab-paclitaxel has significant antitumor activity as a single agent in experimental pancreatic cancer and can also enhance gemcitabine effects in combination. These findings provide a strong rationale for testing nab-paclitaxel in patients with pancreatic cancer.

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Is Long-term Survival Possible in Resectable Pancreatic Cancer? W.R. Burns,* J. Tosoian, N. Rezaee, R.H. Hruban, J.L. Cameron, T.M. Pawlik, M. Choti, R.D. Schulick, B.H. Edil, N. Ahuja, A. Maitra, C. Iacobuzio-Donahue, C.L. Wolfgang. *Johns Hopkins Hospital, Baltimore, MD.*

Introduction: Pancreatic cancer is an aggressive disease with poor survival. However, some patients experience substantial survival following surgical resection. Our aim was to better understand these long-term survivors and identify their unique clinical and pathologic characteristics. Methods: Patients with pancreatic cancer who underwent a potentially curative resection from 1970 to 2001 were identified from a single institutional database. Pathology was limited to pancreatic adenocarcinoma; other periampullary and pancreatic neoplasms were excluded. Results: The study included 797 patients with a median age of 65.4 years – 54% were male and 86% were white race. 94 patients (11.7%) survived at least 10 years following surgical resection. The median survival for the long-term survivor group was 12.7 years, compared to 1.2 years for the remainder of the cohort. In comparison to 703 patients who survived less than 10 years, the long-term survivors were younger at diagnosis (61.7 vs. 65.9; p=0.0004) and had fewer comorbidites (coronary artery disease, p = 0.028; hypertension, p=0.024; diabetes, p=0.027). Long-term survivors had smaller tumors (median; 2.54 vs. 3.23 cm; p=0.0002), lower rates of lymph node metastases (59% vs. 76%; p<0.0001), lower lymph node ratios (0.11 vs. 0.23; p<0.0001) and higher rates of margin free of tumor (R0), (59% vs. 37%; p=0.001). On multivariate analysis, age (p<0.001), tumor size (p=0.003), nodal metastases (p=0.005) and margin status (p=0.007) were all associated with long-term survival. In contrast, perineural invasion (p=0.318) and microvascular invasion (p=0.153) were not associated with long-term survival. 59% of long-term survivors had lymph node metastases while 23% had a microscopic positive margin (R1) resection. Conclusion: Long-term survival can be achieved in patients who undergo a potentially curative resection of pancreatic adenocarcinoma. Long-term survivors have smaller tumors, lower rates of lymph node metastases, and less frequent margin involvement. These finding suggest earlier detection, favorable tumor biology, or both. Interestingly, neither nodal metastases nor margin involvement with invasive cancer precludes long-term survival.

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Role of Cytoreductive Surgery for Peritoneal Carcinomatosis for Gastric Cancer L.A. Espino-Urbina, H. Medina-Franco,* L.A. Martín-del-Campo. *National Institute of Medical Sciences and Nutrition "Salvador Zubiran", Mexico City, DF, Mexico.*

BACKGROUND. Recently, intraperitoneal hyperthermic chemotherapy (HIPEC) after cytoreductive surgery (CRS) has been found to prolong survival in patients with peritoneal cancinomatosis for gastric cancer. The objective of this study was to evaluate the role of CRS alone in this group of patients. METHODS: Eight hundred and sixty two patients diagnosed with gastric cancer from January 1984 through December 2010 in a tertiary referral center in Mexico City were included in a retrospective study. A subset of 470 patients (54.5%) were classified as Stage IV according to the American Joint Committee on Cancer (AJCC-TNM 7th edition). We evaluated patients who underwent CRS. Survival curves were constructed with the Kaplan-Meier method. Comparison between groups were calculated with Chi-square test and p<0.05 was considered statistically significant. RESULTS: One hundred and thirteen patients (24.04%) underwent CRS. Median patient age was 57 years (range, 15-90) and 59% were women. Survival for patients who underwent CRS was 14.5 months vs. 6.1 months for those who did not (p<0.0001). Survival was significantly associated with the completeness of cytoreduction: median survival was 22, 17 and 8 months for R0, R1 and R2, respectively (P<0.0001 for R0 vs. R2). D2 was associated with better survival than D1 lymphadenectomy (20 vs. 12 months; p=0.034). Most patients received systemic chemotherapy but no patient underwent HIPEC. Morbidity was 53% but most of them were minor complications. Thirty-day surgical mortality was 7.9% and median length of hospital stay was 20.7 days. In addition to lack of complete CRS, other variables associated with poor survival were poor performance status (Karnofsky<70), low serum albumin, lymph node ratio > 33%, lymphocites <1500 cels/ml, BMI <19 kg/mt2 and serum CEA >10 ng/dl (P<0.05). CONCLUSION: CRS alone for peritoneal carcinomatosis from gastric cancer was assocaited with survival benefit. The reported survival equates reported in the literature with the use of CRS and HIPEC. Despite the retrospective nature of the study, the results call into question the role of HIPEC on the survival of such patients.

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Effect of Antecolic versus Retrocolic Reconstruction of Gastrojejunostomy on Delayed Gastric Emptying Following Classic Whipple Procedure: A Prospective Randomized Trial A. Siripong,* M. Chung, C. Mascarenhas. *General Surgery, Grand Rapids Medical Education Partners, Grand Rapids, MI.*

Background: Delayed gastric emptying (DGE) is a common complication seen after pancreaticoduodenectomy (PD). Previous studies have demonstrated that antecolic duodenojejunostomy decreased the incidence of DGE after pylorus-preserving PD. The objective of our study was to investigate the effect of antecolic (AC) versus retrocolic (RC) gastrojejunostomy (GJ) on DGE in the setting of a Classic Whipple (CW) procedure in a randomized prospective trial. Methods: An IRB approved prospective randomized study was instituted at a single institution. Patients with benign and malignant pancreatic pathology needing a CW were randomized into the antecolic or retrocolic GJ procedure. Primary outcomes were incidence of DGE and number of days until tolerating oral intake. Secondary outcomes included length of stay and postoperative morbidity. Results: 40 patients were enrolled, with 22 and 18 patients in the AC and RC groups. One patient was excluded, for a total of 39 patients included in the analysis. Both groups had similar demographic, preoperative, and intraoperative data including age, gender, estimated blood loss, and comorbidities. 37 of 39 patients had malignant pathology. Overall, there was a 35.9% incidence of DGE, with no significant difference seen between the AC (29.4%) and RC (40.9%) groups (p=0.46). Although not statistically significant, analysis with Kaplan-Meijer curves demonstrated a trend for fewer number of days until tolerating oral intake in the AC compared to RC group (3 vs. 15 days; P=0.84). No significant association was found between incidence of pancreatic leak (10.5%) or abscess (10.3%) and DGE. Conclusion:

Our results suggest that anatomic location of the GJ reconstruction in the setting of a CW does not play a significant role in the incidence of DGE, although a larger study in the future may be needed to confirm these findings.

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Influence of Preoperative Chemoradiation on Biologically Significant Parameters in Ampullary Carcinoma C.L. Roland,* M.H. Katz, G.M. Gonzalez, P.W. Pisters, J. Vauthey, C. Crane, J.E. Lee, J.B. Fleming. *MD Anderson Cancer Center, Houston, TX.*

Introduction: We have previously reported the benefits of preoperative chemoradiation in patients with pancreatic adenocarcinoma. Our hypothesis is that preoperative chemoradiation will influence known prognostic factors in ampullary carcinoma (AC). To address this question, we compared factors and outcomes in patients with AC who got preoperative or postoperative chemoradiation + pancreaticoduodenectomy (PD) versus PD alone. Methods: A prospective tumor registry database was queried to identify patients who underwent PD +/- preoperative (preCRT) or postoperative chemoradiation (postCRT) between 1995 and 2011. Clinicopathologic features were correlated with disease-free survival (DFS) and overall survival (OS) using univariate Cox proportional hazard models. Results: The study population was comprised of 33 patients who received preCRT, 34 patients who had postCRT and 77 who had PD alone. Estimated rates of actuarial 1-year and 3 year OS were 97% and 75%, respectively. There were no differences in tumor size, surgery time, estimated blood loss, T stage, number of lymph nodes retrieved or complications between the groups. preCRT patients were significantly less likely to have lymphovascular invasion (LVI) than postCRT or PD patients (25% vs 56 and 52%, respectively; p=0.05). For the study population only T stage, LVI and increasing number of positive lymph nodes were predictors of OS and DFS (Table 1). However, for preCRT patients, only LVI and increasing number of positive lymph nodes had a significant effect on OS and DFS. Conclusions: This is the first report demonstrating significant differences in LVI for patients undergoing preoperative chemoradiation for AC. Advanced primary tumor stage, LVI and increasing number of positive lymph nodes were associated with inferior OS and DFS after PD for AC. Although preoperative chemoradiation did not impact survival, patients undergoing treatment with preoperative chemoradiation were significantly less likely to have LVI on final pathology, which was a significant predictor of OS and DFS.

Proportional Hazards for Overal Survival

	N	No. deaths	Median Overall Survival (Months)	Hazard Ratio (95% CI)	P-value
T Stage					0.008
T0	4	1	NR	ref.	
T1	26	10	120	2.04 (0.26-15.98)	
T2	51	17	172	1.55 (0.20-11.4)	
T3	38	19	60	3.22 (0.43-24.18)	
T4	25	16	39	4.87 (0.64-37.16)	
LVI					0.001
Negative	61	21	146	ref.	
Positive	54	28	56	2.77 (1.52-5.05)	
# positive LN	144	63	108.32	1.19 (1.08-1.32)	0.001

NR=not reached

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Survivin is a Potential New Therapeutic Target in the Treatment of Pancreatic Cancer Q.P. Ly,* J.J. Person, C.A. Teggart, M.R. Mathiesen, G.M. Howell, M.G. Brattain. *Surgery, University of Nebraska Medical Center, Omaha, NE.*

BACKGROUND: Pancreatic cancer has the grimmest prognosis due to the lack of effective systemic therapies for advanced disease. Survivin indirectly inhibits apoptosis by stabilizing XIAP, an inhibitor of caspase activation. Importantly, survivin is highly expressed in most human tumors and fetal tissues, but is completely absent in matured, differentiated cells. Recently, YM155, a small molecule inhibitor of survivin transcription, has been shown to be effective in inducing apoptosis in a variety of tumor cell lines and xenografts but it has not been studied in pancreatic cancers. In this study, we showed that YM155 inhibits cell proliferation and induces apoptosis in both Smad4 wild-type and mutant pancreatic cell lines in vitro and in vivo. METHODS: MiaPaCa2 and CFPAC cell lines were used to test YM155 activity in vitro. With the approval of our IACUC, we implanted MiaPaCa2 and CFPAC xenografts in athymic nude mice and treated the animals with YM155 to study the in vivo efficacy of the drugs. The xenografts were harvested for biochemical marker studies with Ki-67 and TUNEL staining. RESULTS: Both MiaPaCa2 and CFPAC responded to YM155 treatment with decreased proliferation at similar IC50 of 25nM and inducing apoptosis at similar dose concentration (figures 1A and 1B). Both MiaPaCa and CFPAC xenografts have decreased tumor growth rate when treated with YM155 at 5mg/kg/day with an osmotic pump (figure 1C and 1D). As with the in vitro data, Ki-67 staining was decreased while TUNEL staining was increased in treated xenografts compared to the lactic acid vehicle control tumors, confirming decreased cell proliferation and increased apoptosis in YM155 treated tumors, respectively. CONCLUSIONS: Inhibiting survivin is efficacious in decreasing cell proliferation and increasing apoptosis in both smad4 wild-type and mutant pancreatic cancer cell lines in vitro and in vivo. YM155 has been shown to be safe in several phase I and phase II clinical trials in solid tumors such as prostate, lung and melanoma. Our data provide strong evidence that survivin maybe a potential therapeutic target in the treatment of pancreatic cancers.

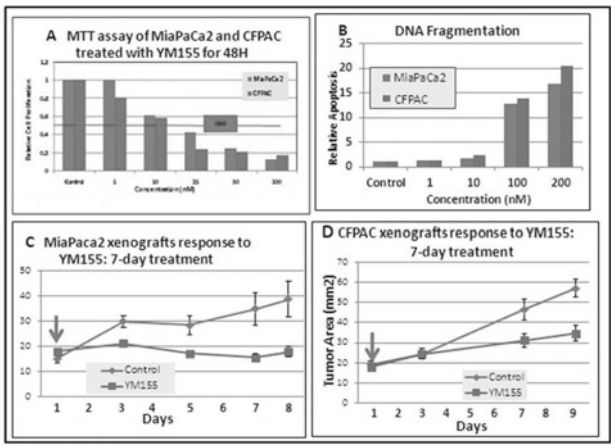

Figure : Relative Proliferation and Apoptosis of MiaPaCa2 and CFPAC in response to YM155.
(A) showed MTT of the two cells (Smad4 wt and mutant PaCa cell lines) treated with YM155 for 48hrs. (B) showed DNA fragmentation of the two cell lines in response to YM155 also for 48 hours
(C) showed MiaPaCa2 and (D) CFPAC xenografts treated with YM155 at 5mg/kg/day continuous SQ infusion.

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Initial Experience and Oncologic Outcomes in Patients undergoing Robotic-assisted Ivor-Lewis Esophagogastrectomy S.G. De la Fuente,* J.M. Weber, S.E. Hoffe, R. Shridhar, K. Almhanna, R.C. Karl, K.L. Meredith. *H. Lee Moffitt Cancer Center, Tampa, FL.*

Background: The introduction of robotic systems to surgical oncology has allowed improved visualization with more precise manipulation of tissues. In esophageal cancer patients, this is crucial since most patients undergo neoadjuvant therapy (NT) prior to surgical resection. We report our initial experience in patients undergoing robotic-assisted Ivor-Lewis esophagogastrectomy (RAIL) for oncologic purposes at a large-referral center. Methods: A retrospective review of all consecutive patients undergoing RAIL from 2010-2011 was performed. Basic demographics such as age, gender, and body mass index (BMI) were recorded. Oncologic outcomes include tumor type, location, NT, postoperative tumor margins, and nodal harvest. Immediate 30-day postoperative complications were also recorded. Results: We identified 50 patients who under went RAIL with median age of 66 (42-82 years). The mean BMI was 28.6 ± 0.7, 67% of patients received NT and 54% had an ASA classification of 3. The mean and median number of lymph nodes retrieved during surgery was 20 ± 1.4 and 18.5 (8-63) respectively. R0 resections were achieved in all patients. The mean estimated blood loss was 146 ± 15 ml and there were no conversions to an open procedure. Postoperative complications occurred in 13 (26 %) of patients. Complications included atrial fibrillation 5 (10%), pneumonia 5 (10%), anastomotic leak 1 (2%), conduit staple line leak 1(2%), and chylous thorax 2 (4%). There were no wound infections documented. The median ICU stay and length of hospitalization (LOH) were 2 and 9 days respectively. Total mean operating time calculated from time of skin incision to wound closure

was 453 ± 13 minutes. The mean operative time significantly decreased over time (first 23 cases 479 min vs. second 23 cases 428 min, p<0.05). Similarly the frequency of complications decreased significantly after 28 cases: 10 (35%) vs. 3 (13%) p=0.04. There were no in hospital mortalities. Conclusions: We demonstrated that RAIL for esophageal cancer can be performed safely with acceptable oncologic outcomes. RAIL may be associated with fewer complications after a learning curve, and shorter ICU stay and LOH.

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Have Outcomes in Gastric Adenocarcinoma Improved over the Last Decade? A 20-Year Retrospective Review S. Anantha Sathyanarayana,[1]* G.B. Deutsch,[1] M. Akerman,[2] L.J. Auguste.[1]
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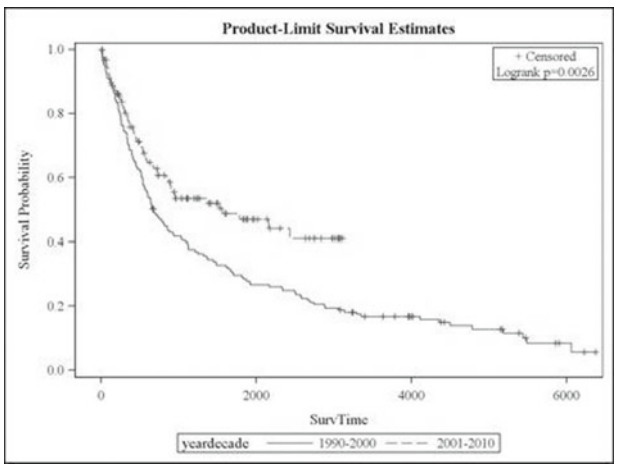
Introduction: Although the incidence of gastric cancer has decreased over the last several decades, it continues to be worldwide the second most common cause of cancer death. While much of the current literature focuses on the adjuvant and neoadjuvant treatment of gastric cancer, there remains a relative paucity of longitudinal studies. We set out to review our institutional data from the last two decades to ascertain any improvement in the outcomes of gastric cancer. Methods: Data collected on 297 patients with gastric adenocarcinoma from a tertiary care hospital tumor registry were analyzed retrospectively. They were divided into Group 1 (1990-2000) and Group 2 (2001-2010), based on the date of surgery. Mann-Whitney and chi-square tests were used to compare groups. The Kaplan-Meier Product-Limit Method was used for survival analysis and the distributions were compared using the log-rank test. A result was considered significant at the p<0.05 level. Results: The average age of our population was 69 years, with 65% males in both groups. Tis, T1, T2 lesions increased, T3, T4 lesions decreased, and M1 lesions shrunk significantly in Group 2. There was a significant survival benefit in both decades for lower values of T (p<0.0001 and 0.0027), N (p<0.0001 and 0.017), and M staging (p<0.0020 and 0.027). Considering overall stages, 49% of patients had Stage 3+ disease at diagnosis in Group 1, compared to 30.4% in Group 2 (p<0.001/0.0089), The average number of nodes dissected was 10 and 15 (p 0.00014) and nodal positivity was 3.7 and 3.5 (p 0.212) for Groups 1 and 2, respectively. Although there was no statistical significance, there was a trend towards increased use of adjuvant chemo-radiation in Group 2. The main difference between both groups was an improved 5-year survival of 47% vs. 29%. (Figure1). Conclusion: We have demonstrated an improvement in survival over the last decade in patients with gastric carcinoma. While this may be the result of earlier diagnosis and more radical nodal dissections, it is unclear if the trend towards increased use of adjuvant chemo-radiation contributed to this striking difference.



Kaplan-Meier survival curves for gastric cancer patients: 1990- 2000 and 2001-2010

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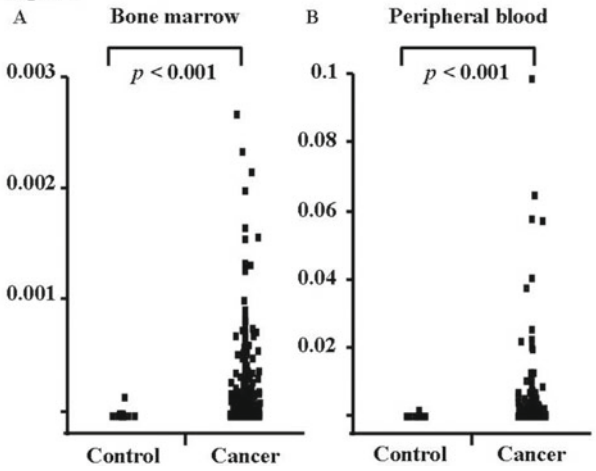
Clinical Significance of Molecular Detection of Matrix Metalloproteinase-1 in Bone Marrow and Peripheral Blood in Patients with Gastric Cancer Y. Kosaka,[1]* K. Mimori,[2] T. Fukagawa,[3] K. Ishikawa,[2] T. Etoh,[3] H. Katai,[3] T. Sano,[3] M. Watanabe,[1] M. Sasako,[3] M. Mori.[4]
1. Kitasato Univ., Kanagawa, Japan; 2. Kyushu University, Oita, Japan; 3. National Cancer Center Hospital, Tokyo, Japan; 4. Osaka University, Osaka, Japan.

Purpose: Matrix metalloproteinases are responsible for the proteolytic degradation of the basement membrane and extracellular matrix. In tumor tissues, elevated expression of matrix metalloproteinase-1 (MMP-1) has been associated with tumor invasion and metastasis. However, little is known about the expression of MMP-1 in peripheral blood (PB) and bone marrow (BM) in gastric cancer patients. Thus, the aim of the present study was to determine MMP-1 mRNA expression levels in the BM and PB of patients with gastric cancer. Methods: The study group consisted of 857 patients with gastric cancer (577 males and 280 females) ranging in age from 27 - 87 years (average age 61.6). MMP-1 mRNA expression levels in BM and PB were evaluated quantitatively by real- time RT-PCR. Results: Expression of MMP-1 mRNA in BM and PB of patients with gastric cancer was significantly higher than in non-cancer patients. High levels of MMP-1 mRNA expression were significantly associated with differentiated histology, tumor size, tumor invasiveness, lymph node metastasis, liver metastasis and the clinical stage. Particularly important, MMP-1 mRNA expression in PB was an independent factor of distant metastasis. Conclusions: We disclosed that MMP-1 mRNA expressions in peripheral blood and bone marrow of gastric cancer patients were very high level. There were shown the staging of gastric cancer precisely. MMP-1 mRNA expression in peripheral blood may be a useful marker for distant metastasis in gastric cancer.

Figure 1



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Fear of Cancer Recurrence and Quality of Life among Survivors of Pancreatic and Periampullary Neoplasms M.Q. Petzel,[1]* N.H. Parker,[1] A.D. Valentine,[2] S. Simard,[3] G.N. Nogueras-Gonzalez,[4] J.B. Fleming,[1] J.E. Lee,[1] P.W. Pisters,[1] J. Vauthey,[1] M.H. Katz.[1]
1. Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; 2. Psychiatry, The University of Texas M. D. Anderson Cancer Center, Houston, TX; 3. Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Quebec, QC, Canada; 4. Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

Background: Fear of Cancer Recurrence (FCR) is well documented among survivors of breast, colon and prostate cancer. Incurable recurrence is common following resection of pancreatic and periampullary neoplasms. The incidence and significance of FCR in this population is unknown. We hypothesized that FCR represents an important source of psychosocial distress following resection of pancreatic neoplasms. Methods: We conducted a cross-sectional

study of patients with non-recurrent pancreatic ductal (PDAC), periampullary adenocarcinoma or pancreatic neuroendocrine tumor (PNET) treated with potentially curative surgery 1991–2011. We assessed 7 discrete dimensions of FCR using the Fear of Recurrence Inventory (FCRI) and evaluated quality of life (QOL) and psychosocial distress using the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire and Hospital Anxiety and Depression Scale. Participants completed these validated instruments by mail. Results: 188 (53%) of 355 eligible patients completed at least one instrument, a median of 49 months (range, 6–222 months) following potentially curative resection. Participants included 73 (39%) patients with PDAC, 55 (29%) with periampullary adenocarcinoma, and 60 (32%) with PNET. The median FCR severity score was higher than a previously established cutoff for clinical significance in 55%, 51% and 63% of patients with PDAC, periampullary adenocarcinoma and PNET, respectively. Older age, male gender, periampullary adenocarcinoma, negative lymph nodes, and longer interval since operation were clinical factors associated with lower total FCR score (all $p<0.05$). In multivariate analysis, only age ($p=0.01$) and gender ($p=0.03$) were independently associated with severity of FCR. A higher total FCR score was significantly associated with higher anxiety ($r=0.64$), depression ($r=0.41$) and lower QOL ($r=-0.53$), all $p<0.001$. Conclusion: Fear of cancer recurrence is pervasive following resection of pancreatic neoplasms, regardless of survivors' histopathologic diagnosis, disease severity, or time since resection. Given its association with anxiety, depression and lower QOL, FCR represents a critical therapeutic target.

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Histone Deacetylase Inhibitor, Vorinostat, as an Enhancer of Gemcitabine Therapy for Resistant Pancreatic Tumors L.J. Green,* N. Koshkina, S.A. Curley. *Surgical Oncology, M.D. Anderson Cancer Center, Houston, TX.*

Introduction: Because of the delay in diagnosis and chemotherapeutic resistance, overall 5-year survival rates of patients with pancreatic cancer remains below 15%. We hypothesize that 1) vorinostat (suberoylanilide hydoxamic acid) will improve efficacy of gemcitabine in gemcitabine-resistant pancreatic tumor cells; and 2) vorinostat works through determine the role of inhibitors of apoptosis proteins (IAPs) in cellular response to this agent alone and in combination with gemcitabine. Methods: Six different human pancreatic cell lines were treated with various levels of vorinostat with or without gemcitabine. Viability of tumor cells was determined via MTT assay. Cytoplasmic levels of IAPs, including survivin, were analyzed via western blot assay. Intracellular localization of survivin was determined using immunohistochemistry and fluorescence microscopy. All assays were preformed in triplicate. Results: Combinations of vorinostat with gemcitabine significantly inhibited pancreatic cancer cells growth in vitro when compared with either treatment alone (p value=0.00004). Cell lines with low sensitivity to gemcitabine, such as Panc-1, Vorinostat reversed the resistance and made them susceptible. Screening of IAPs expression in tumor cells after exposure to vorinostat revealed variation of their expression in pancreatic tumor cells except survivin, whose expression declined consistently in all cells after vorinostat treatment. Immunohistochemical analysis with fluorescence microscopy indicated the translocation of survivin to the nucleus. Overall cytoplasm levels of survivin were seen to decline across all cell lines treated. Conclusion: We conclude that 1) vorinostat increases the efficacy of gemcitabine on pancreatic cells; and 2) decline of survivin protein levels in the cytoplasm and its translocation to the nucleus in cancer cells after exposure to vorinostat indicated that survivin plays an important role in improving the chemotherapeutic effect of gemcitabine. We are currently conducting in vivo experiments to verify our findings using orthotopic pancreatic tumor animal models.

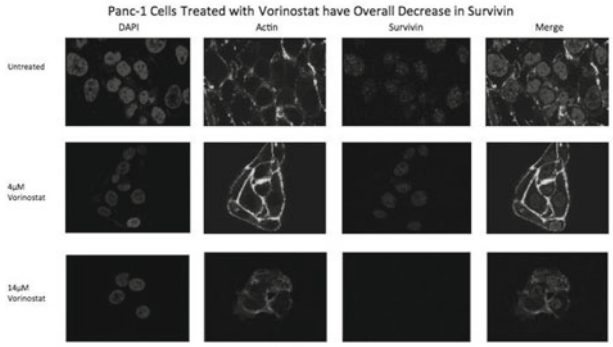

Figure: Confocal fluorescence microscopy. Panc-1 cells were treated with various levels of vorinostat and incubated for 72 hours. Cells were then fixed and incubated with survivin antibody and stained with AlexaFluor 647 (red, survivin), Alexaflour 488(green,actin) and DAPI (blue, DNA) and imaged under confocal fluorescence microscopy. With increasing doses of vorinostat, overall levels of survivin are shown to decrease, including nuclearization of survivin. This is likely the mechanism for the increase in gemcitabine toxicity when Panc-1 cells are exposed to gemcitabine and vorinostat in combination.

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WITHDRAWN

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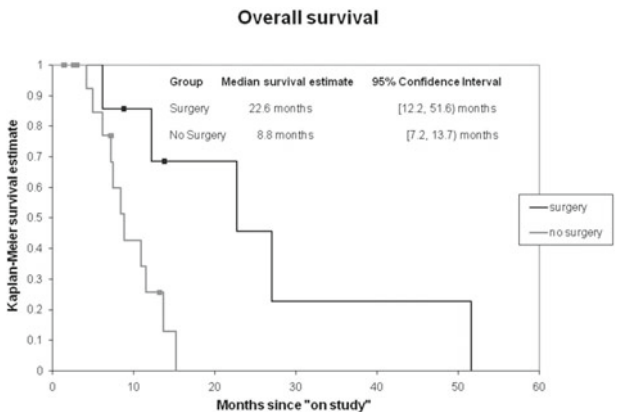
Neoadjuvant Interferon-based Chemoradiation for Locally Advanced Pancreas Cancer: A Phase II Pilot Study E.H. Jensen,[1]* L. Armstrong,[1] S.M. Vickers,[1] T.M. Tuttle,[1] T. Sielaff,[2] E.W. Greeno.[1] *1. Surgery, University of Minnesota Medical Center, Minneapolis, MN; 2. Abbott Northwestern Hospital, Minneapolis, MN.*

Background: Neoadjuvant chemoradiotherapy (CRT) is a viable treatment strategy for patients with locally advanced pancreas cancer. We evaluated the Virginia Mason Protocol (5-fluorouracil, cisplatin, interferon-α and radiation) given in the neoadjuvant setting for the treatment of locally advanced pancreatic cancer. Methods: We performed a phase II pilot study including patients with locally advanced pancreas cancer, including borderline resectable and initially non-resectable cases. Patients with evidence of metastases, previous chemotherapy, ECOG performance status >1, or inadequate hematologic, renal or hepatic function were excluded. Results: We enrolled 23 patients between 1/2005 and 10/2010. Mean age at enrollment was 58.6 years. Males made up 73.4% of the cohort. Of 23 patients, 7 (30.4%) completed all treatments. The remaining 16 (69.6%) patients did not receive all scheduled treatments due to severe side effects (n=7, 30.4%), progressive disease (n=3, 13%), alternative treatment (n=3, 13%), patient withdrawal (n=1, 4.3%), other disease (n=1, 4.3%), and death on study (n=1, 4.3%). Hospitalization was required due to toxicity for 47.8% (n=11) of patients. The most commonly reported grade 3 or 4 toxicities were leucopenia/cytopenia (n=19, 82.6%) and gastrointestinal (n=19, 82.6%). Other toxicities were much less common (fatigue, weight loss, pain, skin rash, all n<3). No tumor regression was seen following neoadjuvant CRT. Surgical resection was ultimately successful in 7 (30.4%) cases. Surgical margins were negative in 6 of 7 cases (85.7%). The mean lymph node count was 11. Positive lymph nodes were identified in 3 of 7 cases (42.8%). Overall survival for all patients was 11.5 months. Surgical resection provided significantly improved survival (22.6 months) compared to CRT alone (8.8 months). Disease free survival in resected patients was 17.2 months. Conclusion: Aggressive neoadjuvant CRT with immunotherapy may allow for resection of initially non-resectable, locally advanced pancreas cancer, but with significant toxicity. Overall survival was similar to other, less toxic regimens. In the absence of surgical resection, survival remains dismal.



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Changes in BMI During Preoperative Therapy Predicts Treatment and Survival Outcomes in Pancreatic Cancer V. Sohn,* M. Petzel, H. Lin, M. Katz, L. Jeffrey, J. Fleming. *MD Anderson Cancer Center, Houston, TX.*

Introduction: Administration of preoperative therapy to patients with potentially resectable (PR) head of pancreas adenocarcinoma (PAC) has several documented advantages. However, one potential disadvantage is the worsening nutritional derangements of these often malnourished patients. Furthermore, patients who receive curative surgery continue to have feeding difficulties in the post-operative setting. In this study, we sought to characterize patterns of weight change with preoperative therapy and identify the impact of these changes on outcomes. Methods: The records of all patients with PR PAC who received preoperative chemo and/or chemoradiation at our institution from 2002-2007 were reviewed. Patients were divided into two cohorts depending on whether or not they proceeded to curative resection after completing preoperative therapy. Univariate and multivariate analysis was performed. Weight change was expressed as percent change in BMI (kg/m2). Results: Of the 172 patients, 117 (68%) proceeded to surgical resection and 55 (32%) were not candidates because of development of metastatic disease (46, 84%), local disease progression (8,15%), or no response to therapy (1, 1%) . Patients undergoing surgery experienced less weight change (0.32% change in BMI from time of presentation) compared to those who did not proceed with surgery (-4.74%; $p<0.001$). Among the cohort of resected patients, median weight loss at approximately the 3, 6, and 12 month post-op period were 8.22, 7.70, and 6.34% from pre-surgery BMI. Weight loss >15% BMI correlated with a shorter time to development of metastatic disease (95% confidence interval (CI) = 0.23 (0.07, 0.749), p = 0.0147) and inferior recurrent free survival (95% CI = 0.191 (0.068, 0.537), p = 0.0017). Changes in BMI at presentation or after preoperative treatment did not impact OS ($p>0.31$). Conclusion: Among patients with PR PAC, ongoing weight loss may be predictive of preoperative failure. Additionally, ongoing weight loss >15% of initial BMI was associated with worse outcome. On average, most patients were not back to pre-operative BMI one year after curative resection for pancreatic cancer.

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Lymph Node Harvest for Squamous Cell Cancer of the Esophagus Does Not Impact Survival J.L. Deneve,* J.M. Weber, S. Hoffe, R. Sridhar, K. Almhanna, J. Barthel, R.C. Karl, K.L. Meredith. *Surgical Oncology, Moffitt Cancer Center, Tampa, FL.*

Background: The optimal number of lymph nodes harvested remains controversial in patients with esophageal cancer. Pathologic response to neoadjuvant therapy (NT) has demonstrated improved survival. However, little is known regarding the impact of NT or nodal harvest in patients with squamous cell carcinoma (SCC) of the esophagus. We examined the extent of LN harvest and outcome in patients who underwent esophagectomy for SCC. Methods: After IRB approval, using a comprehensive esophageal cancer database we identified patients who underwent esophagectomy between 1994-2011. Clinical and pathologic data were compared using Fisher's exact and chi-square when appropriate while Kaplan-Meier estimates were utilized for survival analysis. Nodal strata were set at 12 (ST-1), 15 (ST-2), and 20 nodes (ST-3). Pathologic response to NT was defined as complete (pCR), partial (pPR), or non-response (pNR). Results: We identified 76 patients who underwent esophagectomy for SCC between 1994-2011. The median age was 62.5 years (40-85 months) with median follow up of 18.5 months (1-157 months). 48 (63%) were male and 28 (37%) were female. Twenty-eight patients (37%) underwent primary esophagectomy alone (PE) while 48 (63%) patients were treated with NT. Extent of lymphadenectomy had no significant impact on overall survival (OS) or disease free survival (DFS) for the entire cohort ST-1 p=0.8 and p=0.9, ST-2 p=0.5 and p=0.4, and ST-3 p=0.5 and 0.4, respectively. Among the patients who received NT, pCR was observed in 28 (58%), pPR in 14 (29)%, and pNR in 6 (13)%. When examining the degree of pathologic response to treatment, extent of LN harvest had no significant impact on OS or DFS for patients who underwent esophagectomy after NT (p=ns across all strata). Conclusion: The extent of LN harvest failed to demonstrate an overall or disease free survival benefit in patients with squamous cell carcinoma of the esophagus. Moreover, patients treated with NT also did not benefit from increased nodal resection irrespective of their pathologic response.

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Margin Status and Neoadjuvant Chemoradiation in Patients with Borderline Resectable Pancreatic Cancer P. Papavasiliou,[1]* J.R. Piposar,[2] R. Arrangoiz,[1] K.T. Chen,[1] F. Zhu,[1] Y. Chun,[1] J.P. Hoffman.[1] *1. Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. Temple University Medical Center, Philadelphia, PA.*

Introduction: The objective of this study was to examine the effect of margin status and neoadjuvant therapy in determining outcomes for borderline resectable (BLR) pancreatic cancer and how neoadjuvant chemoradiation impacts margin of resection. Methods: A retrospective chart review was conducted to identify patients who underwent resection for BLR pancreatic cancer based on the AHPBA/SSO/SSAT consensus definition. Outcomes including overall survival (OS) and disease free survival (DFS) were determined based on margin status, location of positive margin (artery, vein, or pancreas), and receipt of neoadjuvant chemoradiation. Results: One hundred and three patients who met the definition of BLR pancreatic cancer and underwent resection between April 1993 and July 2010 were reviewed. Mean age at diagnosis was 65 with a median follow up time of 19.7 months. Neoadjuvant chemoradiation was administered in 49.5% of patients. Twenty-five percent of patients underwent portal and/or superior mesenteric vein resection, and 7% hepatic artery resection. Microscopic positive margin rate was 54%. Median OS was 17.2 months for patients with positive margins versus 24.9 months for patients with negative margins (p=0.003). Median DFS was 13.1 months for patients with positive margins versus 18.6 months for patients with negative margins (p=0.001). There was no difference in OS or DFS for patients with positive margins based on location or number of positive margins. Of the patients who received neoadjuvant chemoradiation, 61.7% had a negative margin of resection versus a 38.3% negative margin of resection rate for patients who did not receive neoadjuvant chemoradiation (p=0.02). Among patients with a positive margin, there was no difference in OS or DFS with or without neoadjuvant chemoradiation. Conclusion: A positive margin of resection, irrespective of location or number, is associated with worse outcome in patients with BLR pancreatic cancer. The use of neoadjuvant chemoradiation is associated with higher rates of margin free resection.

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A Standardized Operative Technique for Robot-assisted Distal Pancreatectomy: Maximizing Oncologic Principles M. Daouadi,* A.H. Zureikat, M.S. Zenati, H.A. Choudry, A. Tsung, D.L. Bartlett, A.J. Moser, H.J. Zeh. *Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Although minimally-invasive distal pancreatectomy reduces postoperative pain and morbidity, there is no consensus about technical factors critical to maximize oncologic outcomes.We evaluated a uniform operative technique for robot-assisted distal pancreatectomy(RADP) which adheres to the important oncologic principles of open radical distal pancreatectomy via minimal access. Methods:Retrospective analysis(Jan 2008-July 2011)of 41 RADP with the following standard technical components: pancreatic transection over the splenoportal confluence; lymphadenectomy of left gastric and celiac arteries;en bloc excision of the retroperitoneal fascia; splenectomy. Indications for RADP included 9 benign lesions (21.9%)and 32 malignancies:16

pancreatic ductal cancers and 16 pancreatic neuroendocrine (pNET). Results: Median operative time was 289 (231-360)minutes with 200 ml (100-300)median estimated blood loss. Conversion to open was required for one (2.4%) benign lesion exceeding 11cm diameter.Four patients required blood transfusion in the first 90 days (9.7%).Pancreatic fistulas (16, 39%) were classified by ISGPF:7 grade A(17%),4 B(9.7%), 5C(12%). Ninety day postoperative morbidity included 22 (53%) minor(Clavien I/II) and 8 (19%) major complications (Clavien III only). Although one patient with PNET (2%) had a positive margin, all PDA achieved margin negative status. Median lymph node harvest was 18 (13-20), median lymph node ratio was 0.015(0-0.15). Mean hospital stay was 6.7± 2 days. Sixteen patients met eligibility criteria for adjuvant chemotherapy, of which fourteen (87.5%) were treated at a median of 7.5 weeks postoperatively. Conclusion: Minimally invasive distal pancreatecomy with robotic assistance is safe and feasible. Improved surgical manipulation and visualization with the robotic platform allows for a standardized technique that preserves oncologic principles in a minimal access setting. Multi-institution prospective trials with uniform follow-up are required for meaningful assessment of the comparative effectiveness of open and minimally-invasive surgery for pancreatic tumors.

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What Studies are Appropriate and Necessary for Staging Gastric Cancer? Results of a RAND/UCLA Expert Panel M. Dixon,[1]* R. Cardoso,[1] J. Tinmouth,[4] L. Helyer,[2] C. Law,[1] C. Swallow,[1] L. Paszat,[5] R. McLeod,[1] R. Seevaratnam,[1] A. Mahar,[3] N. Coburn.[1] *1. Department of Surgery, University of Toronto, Toronto, ON, Canada; 2. Department of Surgery, Dalhousie University, Halifax, NS, Canada; 3. Department of Community Health and Epidemiology, Queens University, Kingston, ON, Canada; 4. Department of Gastroenterology, University of Toronto, Toronto, ON, Canada; 5. Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada.*

Background: The approach for staging gastric cancer (GC) patients has not been well defined, resulting in widespread heterogeneity in the application of pre-operative staging modalities. Methods: A multi-disciplinary expert panel of 16 physicians from 6 countries scored 84 scenarios. Appropriateness was scored from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores (AS) from 1-3 were considered inappropriate, 4-6 uncertain, and 7-9, appropriate. Agreement was reached when 11 of 16 panelists scored the scenario similarly. If a scenario was agreed to be appropriate, it was given a necessity score (NS) in the same manner. AS and NS are reported if agreed upon. Results: TNM staging should be determined pre-operatively (AS 7.0-9.0; NS 7.0-9.0). Pre-operative radiological assessment should include a computed tomography (CT)-abdomen, CT-pelvis, and should be performed with a multi-detector CT scanner with 5 mm slices (AS 8.0-9.0; NS 7.0-9.0). All patients should have a pre-operative esophagogastroduodenoscopy (EGD). The endoscopist should biopsy the tumor; document its size, description, location, distance from the GE junction, and any GE junction, esophageal or duodenal involvement. If the EGD report is unclear, the surgeon should repeat it to confirm tumor location (AS 7.5-9.0, NS 7.0-9.0). Endoscopic ultrasound is appropriate prior to endoscopic resection, but not surgical resection (AS 9.0). Diagnostic laparoscopy (DL) should be performed prior to resection of cT3,4 lesions, or multi-visceral resections. DL should include visual inspection of the stomach, diaphragm, liver, and ovaries (AS 8.0-9.0, NS 7.0-9.0). Conclusions: The Gastric Cancer Processes of Care expert panel has made recommendations regarding pre-operative staging modalities in an effort to standardize work up. Standardization could lead to more accurate staging and allocation towards optimal stage-specific treatments.

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Gastric Cancer Surgery in a Low Volume Center: Are Long Term Outcomes Comparable? S. Anantha Sathyanarayana,[1]* G.B. Deutsch,[1] M. Akerman,[2] L.J. Auguste.[1] *1. Long Island Jewish Medical Center/ Hofstra- NSLIJ School of Medicine, New Hyde Park, NY; 2. Feinstein Institute of Medical Research/Hofstra- NSLIJ School of Medicine, Manhasset, NY.*

Introduction: Despite its decreasing incidence, gastric cancer continues to be the second leading cause of cancer death worldwide. Surgery remains the primary therapeutic modality for this aggressive disease. Improved outcomes have been reported recently at high volume cancer institutions. Our goal was to evaluate whether similar results can be expected at lower volume tertiary care centers. Methods: A retrospective analysis of 297 patients with a diagnosis of gastric adenocarcinoma was performed. The data was collected from our institutional tumor registry. All patients underwent gastric resection between 1990 and 2010. Descriptive statistics (means ± standard deviation, medians, and frequencies/percentages) were computed. Standard methods of survival analysis were performed using the Kaplan-Meier Product-Limit Method. Survival distributions were compared using the log-rank test. A result was considered significant at the $p<0.05$ level. Results: The average age of our population was 69.1±12.6 with 65.6% males, 75.76% Caucasians. Survival analyses for T, N, M, stage, and depth of invasion are shown in Table 1. 76.1% of the patients had a defined surgical procedure as their only treatment. 82.7% had no residual tumor at the surgical margin, resulting in a survival benefit over those with positive margins (median survival 3.3 vs. 1.0 years respectively, $p< 0.0001$). The median number of nodes dissected from the adjacent nodal basins was 11(mean of 15.54), while a median of 1 was positive for malignancy (mean of 6.49). There was a trend towards improved survival in patients with more than 15 nodes dissected (median survival 3.8 vs. 2.0 years respectively, $p<0.075$). Overall 5-year survival was 35.4% and 10-year survival was 22%. These figures are comparable with outcomes from several international specialty cancer centers. Conclusion: Gastric cancer can be effectively managed at low volume tertiary care centers with similar long term outcomes compared with high volume cancer centers.

Table 1

Tumor characteristics		Median survival in years(95% confidence interval)	Log rank test p-value
T	Tis	Inestimable(2.6, inestimable)	<0.0001
	T1	7.3 (5.0, 11.3)	
	T2	3.3 (1.9, 5.0)	
	T3	1.2 (1.0, 1.5)	
	T4	1.4 (0.5, 1.8)	
N	N0	5.0 (3.1, 7.5)	<0.0001
	N1	1.6 (1.1, 2.0)	
	N2	1.2 (0.8, 2.2)	
	N3	1.6 (0.5, 3.9)	
M	M0	2.5 (1.9, 3.6)	<0.0001
	M1	0.9 (0.2, 1.4)	
Stage	0	Inestimable(2.6, Inestimable)	<0.0001
	1A	6.9 (3.3, 9.0)	
	1B	5.3 (3.7, 14.2)	
	2	1.9 (1.5, 3.0)	
	3A	1.2 (0.9, 1.9)	
	3B	1.2 (0.7, 3.4)	
	4	1.0 (0.5, 1.6)	
Depth of invasion	Mucosa	13.1 (2.4, 14.9)	0.0015
	Submucosa	9.0 (1.4, 9.0)	
	Muscularis propria	3.1 (1.6, 6.7)	
	Serosa	1.8 (1.2, 2.0)	
	Adjacent /Other organs	1.6 (0.8, 2.5)	
	Metastasis	1.8 (0.2, 3.9)	
	Unknown if metastasis or invasion to adjacent organs	1.7 (1.4, 2.6)	

Overall Survival according to tumor characteristics.

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Processes of Care in Curative Gastric Cancer – A RAND/UCLA Appropriateness Study S. Brar,[1] C. Law,[1] R. McLeod,[1] L. Helyer,[2] C. Swallow,[1] L. Paszat,[4] R. Seevaratnam,[1] R. Cardoso,[1] A. Mahar,[3] L. Yohanathan,[1] A. Bocicariu,[1] M. Dixon,[1]* N. Coburn.[1] *1. Department of Surgery, University of Toronto, Toronto, ON, Canada; 2. Department of Surgery, Dalhousie University, Halifax, NS, Canada; 3. Department of Community Health and Epidemiology, Queens University, Kingston, ON, Canada; 4. Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada.*

Introduction: Processes of care in curative therapy for gastric cancer are ill-defined, have significant variations and may impact patient outcomes. Methods: A multi-disciplinary expert panel (16 physicians, 6 countries) scored 595 scenarios using the RAND/UCLA Appropriateness Methodology. Appropriateness was scored from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores from 1-3 were considered inappropriate, 4-6 uncertain, and 7-9 appropriate. Agreement was reached when 11 of 16 panelists scored the statement similarly. If a statement was agreed to be appropriate, it was given a necessity score in the same manner. Results: D1 lymph

node dissection (LND) was considered appropriate for T1 N0 disease. For all others, D2 LND was considered appropriate and necessary. It was appropriate to assess at least 15 LN. Open gastrectomy was considered appropriate for all patients and necessary for patients with N2-3 disease, while laparoscopic gastrectomy was appropriate for patients with T1-2 N0 disease. Intraoperative pathologic assessment of the proximal margin was considered appropriate for gross margins <5 cm or T3/T4 lesions. If the margin was positive on frozen section, re-resection of the stomach or abdominal esophagus was considered appropriate for N1-3 disease and necessary for N0 disease. Curative resection was appropriate if a patient presented with perforation. Neoadjuvant chemotherapy was considered appropriate for patients who presented with T1-2 N2-3 or T3-4 N0-3 disease with minor symptoms but not with major symptoms. Adjuvant chemoradiotherapy was considered appropriate and necessary for patients with T1-2 N1-3 or T3-4 N0-3 disease . No adjuvant therapy was considered appropriate for patients with T1N0 disease. Conclusions: The above criteria have been found to be appropriate and necessary for the curative treatment of patients with gastric cancer and may be used to improve processes and quality of care.

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Snail and Slug Differentially Affect Pancreatic Cancer Cell Scattering and Motility through β1-integrin and Rho Signaling

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Introduction The Snail family of transcription factors has been implicated in pancreatic cancer progression. We recently showed that Snail (Snai1) promotes membrane type 1-matrix metalloproteinase (MT1-MMP)- and ERK1/2-dependent scattering of pancreatic cancer cells in 3D collagen. Here we examine the role of Slug (Snai2) in regulating pancreatic cancer invasion in 3D collagen. Methods Utilizing inducible pancreatic cancer cells that overexpress either Snail or Slug, we analyzed cell motility, invasion through a collagen matrix, and the affects of β1-integrin and Rho signaling on these processes. Results Although Slug increased MT1-MMP expression and ERK1/2 activity, Slug-expressing cells failed to scatter in 3D collagen. Moreover, in contrast to Snail-expressing cells, Slug-expressing cells did not demonstrate increased collagen binding, collagen-driven motility or α2β1-integrin expression. As RhoGTPases have been implicated in invasion and migration, we analyzed the contribution of Rac1 and Rho signaling to the differential migration and scattering of pancreatic cancer cells. Snail-induced migration and scattering were inhibited by a Rac1 inhibitor and by an siRNA against Rac1. Inhibiting ROCK1/2, which are downstream effectors of RhoA activity, in Slug-expressing cells increased migration and scattering in 3D collagen, and thus phenocopied the effects of Snail in 3D collagen. Moreover, the increased migration and scattering in 3D collagen of Snail-expressing cells and of Slug-expressing cells following ROCK1/2 inhibition were dependent on β1-integrin function. Conclusion Overall, these results demonstrate differential effects of Snail and Slug in pancreatic cancer and identify the interplay between Rho signaling and β1-integrin that regulates scattering and migration of Snail- and Slug-expressing pancreatic cancer cells.

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Laparoscopic Gastrectomy for Gastric Adenocarcinoma: A Single Institution's Experience and Oncologic Outcomes of 65 Consecutive Patients

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Introduction: The application of laparoscopy in the surgical treatment of gastric cancer has become more commonly utilized in recent years. Most of the published series are from Asia and few report on survival. Our objective was to elucidate the safety, efficacy, and oncologic outcomes of laparoscopic gastrectomy in patients with gastric adenocarcinoma. Methods: The medical records of all patients who underwent laparoscopic gastrectomy at our Center between 6/2005 and 8/2011 were retrospectively reviewed. Relevant data analyzed included patient demographics, operative parameters, complications, recurrence, and survival. Results: A total of 65 consecutive patients were identified. Of all laparoscopic procedures, 5 were proximal, 41 were distal, and 19 were total gastrectomies. Median age was 67 years (35-96). Median operative time was 370 min (228-583). Median EBL was 200 ml (10-900). Twenty-eight of the 65 laparoscopic gastrectomy cases employed robotic-assisted D2lymph node dissection. The median number of lymph nodes retrieved was 26. Forty-seven cases included D2 lymph node dissections, 16 cases were D1 dissections, and 2 cases involved D0 dissections. All intended D2 dissections had greater than 15 nodes retrieved. Of the 65 patients with gastric adenocarcinoma, histological staging revealed 1 patient had stage 0 disease, 38 had stage I, 17 had stage II, 7 had stage III, and 1 had stage IV disease. Median hospital stay was 7 days (3-39). Morbidity and 30-day mortality rates were 33% and 3%, respectively. Median follow-up was 15 months (0.5 to 58). Cancer has recurred in 4 patients (6%). The 3 year overall survival for stage I disease is 92%, stage II disease is 71%, and for stage III is 51%. Conclusions: The long-term oncologic outcomes and overall survival are comparable to that of open technique seen in other series. Our large institutional series shows that laparoscopic gastrectomy for gastric adenocarcinoma is feasible and safe and can be performed in patients with excellent surgical and oncologic outcomes.

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Signet Ring Cell Gastric Cancer: Harbinger of Doom?

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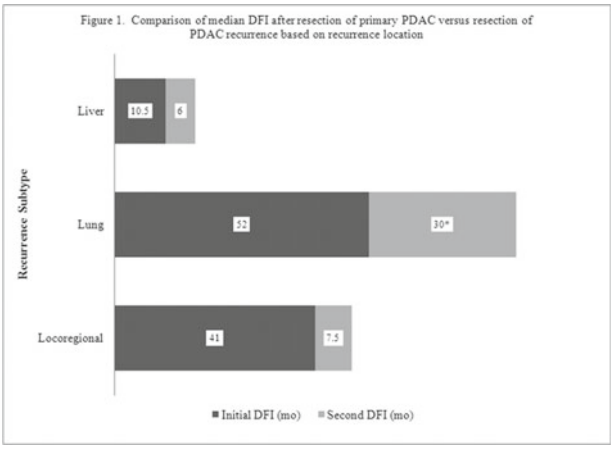
Intro: Signet ring cell gastric carcinoma (SRC) has long been associated with worse prognosis. However, recent studies in Asia have questioned this idea. The aim of this study is to determine differences in presentation and outcomes between SRC and gastric adenocarcinoma (AC) to establish if SRC conveys worse prognosis in the U.S. **Methods:** The NCI Surveillance, Epidemiology and End Results (SEER) program was analyzed for differences in presentation and outcomes of SRC and AC patients from 2004-2007. **Results:** 10,886 cases of gastric cancer included 2,872 SRC and 8,014 AC. SRC presented at younger age (62.0 vs. 68.9 years, p<0.001) and less often in males (53.7 vs. 68.0%, p<0.001). SRC patients were more likely Asian (16.5 vs. 13.5%) or Hispanic (23.3 vs. 14.9%) and less likely Black (10.7 vs. 11.5%) or White (71.8 vs. 74.1%); p<0.001. SRC was more likely to be T-stage 3 or 4 (46.0 vs. 33.8%), have lymph node spread (72.5 vs. 62.0%), and distant metastases (29.0 vs. 24.1%); p<0.001. SRC was more likely to be located in the lower stomach (30.6 vs. 24.6%) or body (30.8 vs. 21.6%) and less likely to be in the upper stomach (24.7 vs. 46.9%); p<0.001. SRC more often overlapped multiple regions (13.9 vs. 6.9%, p<0.001). SRC was associated with increased mortality (HR 1.07, CI 1.01-1.14, p=0.017), and showed decreased median survival (12.0 vs. 13.0 months, p=0.034) by Kaplan-Meir analysis. Multivariate analysis stratified by AJCC stage and radiation treatment demonstrated SRC was not independently associated with mortality (HR 1.04, CI 0.98-1.11, p=0.195). Mortality was associated with age at diagnosis (HR 1.01, CI 1.01-1.01, p=0.001), Black race (HR 1.11, CI 1.02-1.21, p=0.013), and tumor grade (see table). Variables associated with survival included Asian race (HR 0.88, CI 0.81-0.95, p=0.001) and surgery (HR 0.21, CI 0.19-0.22, p=0.001). **Conclusions:** In the U.S., SRC significantly differs from AC in presentation with younger age, less male predominance, greater tumor extent, metastases, and Asian or Hispanic ethnicity. Survival for SRC is associated with Asian race and surgical resection. Overall, SRC survival is less than AC. However, adjusted for stage at presentation, SRC does not portend a worse prognosis.

Signet Ring Cell Carcinoma vs. Adenocarcinoma

Univariate			
Variable	Signet Ring Cell Carcinoma (n=2,872)	Adenocarcinoma (n=8,014)	p-Value
Mean Age, years	62.0 ± 0.2	68.9 ± 0.3	<0.001
Male	53.7%	68.0%	<0.001
White	71.8%	74.1%	0.001
African American	10.7%	11.5%	0.001
Asian	16.5%	13.5%	0.001
Hispanic	23.3%	14.9%	<0.001
Upper Stomach (cardia or fundus)	24.7%	46.9%	<0.001
Body of Stomach (greater or lesser curvature)	30.8%	21.6%	<0.001
Lower Stomach (pylorous or antrum)	30.6%	24.6%	<0.001
Overlapping	13.9%	6.9%	<0.001
T-stage 3 or 4	46.0%	33.8%	<0.001
Lymph Node Mets	72.5%	62.0%	<0.001
Distant Mets	29.0%	24.1%	<0.001
Median Survival, Months	12.0	13.0	0.034
Multivariate Analysis for Mortality (stratified by AJCC stage and radiation vs. AC)			
Variable	Hazard Ratio	95% CI	p-Value
Signet Ring Cell Carcinoma	1.04	0.98-1.11	0.195
Surgical Resection	0.21	0.19-0.22	0.001
Female	0.99	0.94-1.05	0.819
Tumor Grade 2	1.29	1.09-1.53	0.004
Tumor Grade 3	1.74	1.47-2.06	0.001
Tumor Grade 4	1.88	1.50-2.36	0.001
Age at Diagnosis	1.01	1.01-1.01	0.001
African American	1.11	1.02-1.21	0.013
Asian	0.88	0.81-0.95	0.001
Hispanic	0.99	0.92-1.07	0.837
American Indian/Alaskan	0.99	0.72-1.35	0.945



Initial DFI defined as time from resection of primary PDAC to first recurrence and Second DFI defined as time from reoperation to diagnosis of second recurrence. Second DFI in patients with resected lung recurrence reported as mean DFI since median has not been reached in this group (*).

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Selective Re-operation for Locally Recurrent or Metastatic Pancreatic Ductal Adenocarcinoma following Primary Pancreatic Resection R.M. Thomas,* M.J. Truty, J.B. Fleming, P.W. Pisters, J.E. Lee, D.C. Rice, W.L. Hofstetter, R.A. Wolff, G.R. Varadhachary, H. Wang, M.H. Katz. *MD Anderson Cancer Center, Houston, TX.*

Introduction: Resection of recurrent disease in malignancies such as colorectal cancer has been shown to prolong survival but resection for recurrent pancreatic ductal adenocarcinoma (PDAC) is viewed as futile. We sought to identify factors that may be associated with prolonged survival following resection of recurrent PDAC. Methods: A retrospective review of a prospectively-maintained pancreatic tumor database was performed to identify all patients from 1992-2010 who developed recurrent PDAC after intended surgical cure. The group was screened for those who underwent a second operative procedure with curative intent. Clinicopathologic features were correlated with disease-free interval (DFI) and survival to identify factors that may be associated with prolonged survival in patients undergoing reoperation for PDAC. Results: Of 700 patients who underwent resection for PDAC, 426 (61%) recurred after a median of 8mo and 21 (5%) of those had a locoregional [pancreas (n=5), other (n=2)] or distant [lung (n=7), liver (n=6), brain (n=1)] recurrence that were selected for a second, potentially curative operation. Sixteen of 21 patients received chemotherapy prior to reoperation. Those selected had a single, technically resectable lesion, good performance status, and prolonged median DFI compared to patients not selected (22mo v. 8mo, p<0.01). The median DFI from initial resection to recurrence for those with lung (52mo) or locoregional (41mo) recurrence was longer than those with liver recurrence (10.5mo, p=0.03; Fig. 1). The interval between reoperation and second recurrence in patients with lung metastasis (NR) was longer than for liver (6mo) or locoregional recurrence (7.5mo, p=0.02). Patients still alive include 4/7 of lung, 3/7 of locoregional, and 1/6 of liver recurrences with a median follow-up after reoperation of 30mo, 14mo, and 18.5mo, respectively. Conclusions: Patients who develop a solitary recurrence of PDAC in the lung after a long disease-free interval should be considered for reoperation. Those with recurrence in other sites are likely to re-recur relatively quickly after reoperation regardless of disease-free interval.

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What Care is Appropriate and Necessary for Metastatic Gastric Cancer Patients? Results of a RAND/UCLA Expert Panel A. Mahar,[1]* L.K. Helyer,[3] C. Swallow,[4] C. Law,[4] L. Paszat,[5] R. Seevaratnam,[2] R. Cardoso,[2] R. McLeod,[4] A. Bocicariu,[2] N. Coburn,[4] T. Gastric Cancer Processes of Care Expert Panel.[4] *1. Department of Community Health and Epidemiology, Queen's University, Kingston, ON, Canada; 2. Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 3. Department of Surgery, Dalhousie University, Halifax, NS, Canada; 4. Department of Surgery, University of Toronto, Toronto, ON, Canada; 5. Institute for Clinical Evaluative Sciences, Toronto, ON, Canada.*

Background: Most gastric cancer patients present with advanced stage disease precluding curative surgical treatment. The utility of surgical and non-surgical options for non-curative, advanced disease is debated and the appropriate treatment strategy unclear. Methods: A multi-disciplinary expert panel of 16 physicians from 6 countries, scored 47 scenarios using the RAND/UCLA Appropriateness Methodology. Appropriateness was scored from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores (AS) from 1-3 were considered inappropriate, 4-6 uncertain, and 7-9, appropriate. Agreement was reached when 11 of 16 panelists scored the statement similarly. If a statement was agreed to be appropriate, it was then given a necessity score (NS) in the same manner. Results: Surgical resection and bypass were agreed to be inappropriate in patients with minor symptoms and visible carcinomatosis, liver metastases or more than one site of metastatic disease for cardia and distal lesions (AS 1.0-3.5). The expert panel disagreed on the role for surgical resection in patients who were cytology positive only (AS 4-6). The role of resection for patients with major symptoms if they had visible carcinomatosis, liver metastases or more than one site of metastatic disease (AS 2-5) was indeterminant. Patients with distal tumours and major symptoms and multiple liver metastases or more than one site of metastatic disease were considered indeterminant for surgical resection (AS 2). Best supportive care was agreed to be appropriate for patients with minor symptoms and multiple liver metastases or more than one site of metastatic disease (AS 8, NS 5-6). Conclusion: The role of surgery in metastatic gastric cancer treatment decision-making is not supported by experts for the majority of scenarios. Continued uncertainty in appropriate and necessary treatment decision-making for advanced patients with a minimal burden metastatic disease exists and underscores the need for randomized controlled trials.

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The Effect of Total Lymph Nodes Removed and the Lymph Node Ratio on Overall Survival in Resected Pancreatic Cancer C. Wai,* K. Devarajan, J. Hoffman. *Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Previous studies evaluating lymph node status in pancreatic cancer have demonstrated that the ratio of positive nodes to total numbers resected is an important prognostic factor for survival. In our study we sought to see if the total number of nodes removed and lymph node ratio (LNR) would influence overall survival. Method: A retrospective chart review of 210 patients from July 1998 to July 2011 who underwent resection of pancreatic adenocarcinoma was done. Patients were evaluated for demographic information, neoadjuvant therapy status, surgical margins, pathological stage, total number of lymph nodes retrieved and the number of positive lymph nodes. The LNR was calculated by taking the number of positive lymph nodes to the total number of lymph nodes retrieved. The endpoint evaluated was overall survival (OS). Results: Of the 210 patients, 107 (51%) were male and 103 (49%) were female. The median age was 68. A total of 110 patients had 1 or more positive nodes. The median number of nodes evaluated for all patients was 15 (range 2-51) and the median number of positive lymph nodes was 1. In patients with positive lymph nodes, the median LNR was 0.15 or 15%. For the 210 patients, in univariate analysis, there was a statistically significant association between LNR and overall survival. When the LNR reached >11.2%, patient survival was worse (p=0.018). The total number of nodes removed was not significantly associated with OS for those with positive or negative nodes. However, with multivariable CART analysis, taking into account T stage and surgical margins, LNR had a significant impact on overall survival only for patients who had a R0 resection and T0-T2 disease. If their LNR was > 0, survival was better (p=0.043). Conclusions: In certain GI malignancies, complete evaluation of local lymph nodes is important and changes the survival of patients. In T0-T2 stage pancreatic cancer patients resected with negative margins, outcome is worse if there are positive nodes in these patients. Therefore based on our data, the LNR may be useful for determining the prognosis of early T stage cancer patients.

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After Pancreatectomy, Any Rise in CA 19-9 is a Harbinger of Recurrent Pancreatic Cancer and Dismal Survival M.E. McNally,* S. Abdel-Misih, L. Malhotra, S. Albert, C.R. Schmidt, M. Bloomston. *General Surgery, The Ohio State University- The James Cancer Hospital and Solove Research Institute, Columbus, OH.*

Introduction Preoperative serum carbohydrate antigen 19-9 (CA 19-9) is a useful prognostic marker in pancreatic adenocarcinoma (PCA) and its trend is useful in identifying recurrence. We propose that once the CA 19-9 has reached a post-operative nadir, any subsequent rise portends death regardless of clinical disease status. Methods Records from over 1000 patients undergoing pancreatic resection over the last 20 years were reviewed. Of the 381 patients who underwent resection for PCA, 197 had preoperative, post-operative, and post therapy CA19-9 data available. This study focused on only the patients in whom the CA19-9 rose during the observation period. Survival was recorded from the time of any rise in CA19-9 (no matter how slight) after the post-operative nadir until death or last follow-up. Results The median age was 64.9 years in 121 patients (Table). The median survival was 16.2 (3.7-109.4) months. The median survival from nadir was 11.3 (1.2-89) months but after the CA 19-9 rose, survival was only 5.4 months. Most patients rose from their nadir within 6 months (62%; N=75). In this group, most had node positive disease (62%; n=74), negative resection margins (80%; N=96), and lymphovascular or neural invasion (85%; N=103). Conclusion CA 19-9 is a helpful preoperative prognostic marker and can also be useful in following patients after resection and during adjuvant therapy. A rise from nadir, whether post-resection or post-chemotherapy, should be used as an indicator of recurrence or progression and alternative therapy should be considered regardless of clinical status of disease.

Patient Demographics	
Age (years)	64.9 (29.9-84.1)
Male	58.7% (N=71)
Node Positive Disease	62% (N=75)
Neural/LVI*	85% (N=103)
Negative Resection Margins	83.5% (N=101)
Overall Survival (months)	16.2 (3.7-109.4)
Survival after CA 19-9 rise (months)	5.4 (0.07-29.9)
Survival after CA 19-9 nadir (months)	11.3 (1.2-89)
Rise from Nadir in 6 months	62% (N=75)

*Lymphovascular Invasion

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High Quality Pancreas Protocol Computed Tomography Frequently Overestimates the Extent of Disease in Resectable Periampullary Cancers Z. Fong,* H. Lavu, E.P. Kennedy, P.K. Sauter, L.G. Koniaris, E.L. Rosato, C.J. Yeo, J.M. Winter. *Thomas Jefferson University, Philadelphia, PA.*

Introduction: High resolution, triple phase, computed tomography (CT) is a standard preoperative test in patients undergoing pancreatic resection. In the context of advances in imaging, we examined the clinicopathoglic implications of a range of CT findings. Methods: In the past 5 years, 143 patients with resected pancreatic ductal adenocarcinoma (PDA) and 43 patients with resected non-pancreatic periampullary adenocarcinoma (NP-PA) underwent a pancreas protocol CT at our institution. Imaging findings were analyzed with respect to perioperative data. Vessel involvement was defined as any degree of tumor encasement of major visceral vessels. Results: A mass was identified on CT in 94% of PDAs and 74% of NP-PA. In 50% of patients with PDA, there was a discrepancy of ≥1cm between the size of the reported mass and the tumor size in the specimen. The mass size was underestimated in 75% of these cases, and overestimated in 25%. CT was particularly inaccurate at imaging distal bile duct cancers, as 47% were undetectable, despite a median pathologic tumor size of 1.8cm. Enlarged lymph nodes were detected preoperatively on CT in 59% of PDAs. In these patients, 71% had lymph node metastases on pathology. Patients without detectable lymphadenopathy had lymph node metastases in a similar number (73%, p=1.0). This observation is seen in the NP-PA group as well (p=0.8). Vessel involvement on CT was noted in 23% of PDAs. A vessel resection was necessary in 3% of cases with perceived vessel involvement and 2% of cases without involvement (p=0.5). Similarly, there was no difference between the two groups in the rate of a positive uncinate margin (24% vs 27% respectively, p=0.8). Conclusion: While pancreas protocol CT is and should remain a key component of the preoperative evaluation, certain radiographic findings should be interpreted with caution. In particular, lymphadenopathy on CT is not associated with true lymph node metastases. Moreover, in patients selected for surgery, a suggestion of major visceral vessel involvement on CT neither predicts the need for vessel resection, nor is associated with a positive uncinate margin.

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Total Esophagectomy is not Always Necessary in the Surgical Treatment of Malignancy (sq.ca. & adeno.ca.) of the Lower Esophagus and the Cardia R.S. Parikh,[1]* R. Deshpande,[1] R. Mistry,[2] S. Choudhary,[3] J. Medhi,[3] P. Desai.[1] *1. Breach Candy Hospital, Mumbai, Maharashtra, India; 2. Tata Memorial Hospital, Mumbai, Maharashtra, India; 3. Bombay Hospital, Mumbai, Maharashtra, India.*

INTRODUCTION: A left sided thoraco abdominal approach with a radical lower esophagectomy satisfies surgical principles for the treatment of cancer of the lower esophagus and total esophagectomy is not necessary. METHODS: From 1990 to 2005, 330 patients - 186(56%) lower esophageal, 46(14%) cardioesophageal junction and 98(30%) fundus lesions underwent radical lower esophageal resection with anastomosis (esophago-gastrostomy)just under the aortic arch & above left pulmonary hilum through the left thoraco abdominal approach(TAA). TNM classification was used to stage the disease. We demonstrate salient features about the surgical technique of node dissections through the left TAA. This is compared with literature review of total esophagectomy for similar lesions. RESULTS: 8 patients had T1N0, 21 – T2N0, 14 – T1N1, 47 – T2N1, 26 – T3N0, 214 –T3N1. The disease free survival (DFS) & overall survival, the morbidity and mortality rates are nearly similar with both approaches without any statistically significant differences. The DFS in T1N0, T2N0-1, T3N0,1 ranged from 16 to 64% at 5yrs, the morbidity & complications ranged from 13 to 15% and mortality within 3 to 11% in either groups. In locally advanced (T3N1) lesions with involvement of predominantly celiac, para esophageal & perigastric group of nodes, total esophagectomy, transhiatal or transthoracic, with a 3 field nodal dissection does not improve survival and is compatible with significant complications and increased morbidity and mortality. CONCLUSIONS: A left sided TAA is safe, quick & satisfactory in achieving a radical lower esophagectomy and appropriate nodal dissections with acceptable morbidity and mortality in patients with lower esophageal cancers. This procedure should therefore remain in the surgical armamentarium for treatment of this lesion and total esophagectomy is not always necessary.

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Is Laparoscopy Still Needed for Staging "Resectable" Pancreatic Cancer? P.M. Santoro,[1]* R.Z. Abdel-Misih,[2] N.J. Petrelli,[2] J.J. Bennett.[2] *1. Surgery, Christiana Care Health Services, Newark, DE; 2. Helen F. Graham Cancer Center, Newark, DE.*

BACKGROUND: Imaging for pancreatic cancer has demonstrated increased accuracy in staging patients before resection. Many propose diagnostic laparoscopy is therefore unnecessary before laparotomy and resection. Pancreatic cancer still has a high incidence of peritoneal and liver metastases that may be radiographically occult. Our hypothesis is that laparoscopy is still necessary to detect occult disease and avoid non-curative laparotomy in cases of peri-pancreatic malignancy. METHODS: Patient data were collected at a large, academic community-based tertiary care center with a specialized pancreatic team. Retrospective chart review was performed for patients surgically treated for peri-pancreatic neoplasms between the years 2005-2011. Patients with adenocarcinoma were the focus of this study. All patients had triple phase CT imaging for staging and to assess resectability. Patients who had laparoscopy (group 1) were identified and compared to those who did not (group 2). RESULTS: Two hundred and two patients from 2005-2011 with pancreatic neoplasms were identified as radiographically resectable. Of these, 107 had pancreatic adenocarcinoma (53%). In the first group, 80 patients underwent diagnostic laparoscopy (75%) and metastatic disease was identified in 8 cases (10%). Laparotomy for resection was performed for the remaining 72 patients and 6 were found to have metastatic disease that was missed during laparoscopy. The overall prevalence of metastatic disease in this group was 17.5%. In the second group, 27 patients underwent laparotomy without laparoscopy. Four of these patients(15%) were found to have metastatic disease. The sensitivity of laparoscopy to detect radiographically occult metastases was 70%. Laparoscopy still missed 43% (6/14) of patients ultimately found to have metastatic disease in this group. CONCLUSIONS: Occult metastases were still found in 15%-17.5% of patients despite modern CT scan imaging. Even though laparoscopy missed some metastases when compared to laparotomy, our results show that 10% of patients were spared an unnecessary laparotomy. Laparoscopy should still play a role in staging patients with radiographically resectable pancreatic cancer.

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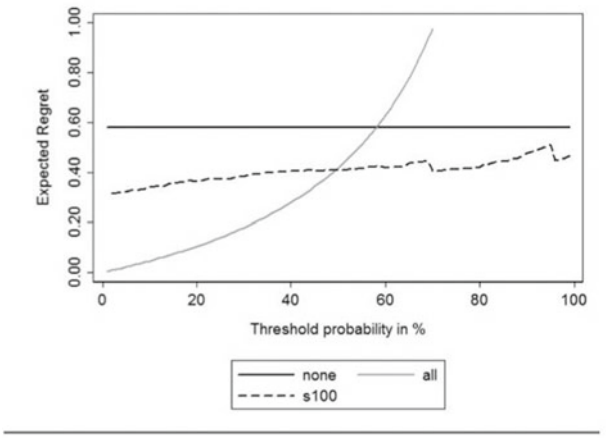
Regret Theory Modeling in Pancreatic Adenocarcinoma J.M. Hernandez,* A. Tsalatsanis, B. Djulbegovic, V. Velanovich. *University of South Florida, Tampa, FL.*

Introduction: Pancreatic adenocarcinoma is uniformly fatal without operative intervention, although resection infrequently results in longterm survival and can be associated with significant morbidity and even mortality. Regret theory serves as a framework linking both rationality and intuition, in order to determine an optimal course of action for physicians facing difficult decisions. Methods: We generated a Cox regression model for patients with pancreatic adenocarcinoma using pretreatment stage, resection, pretreatment vitality, and pathologic stage. We evaluated the model using regret based decision curve analysis, which translates the probability estimated by the model to a decision by taking into account the decision maker's preference expressed in terms of threshold probability. The analysis modeled three possible choices: always perform surgery, never perform surgery, and act according to the prediction model. Results: 153 consecutive patients with pancreatic adenocarcinoma were evaluated by a single surgeon at a tertiary referral center. Preoperative stage (p=0.005, CI 1.19-2.27), resection (p=0.007, CI 0.27-0.82), vitality (p<0.001, CI 0.96-0.98) and pathologic stage (p<0.001, CI 3.06-16.05) were each independent predictors of overall survival. As seen in figure 1, for a threshold probability <50% (decision maker considers failing to operate more regretful than unnecessary surgery), the optimal decision is to operate on all patients irrespective of the model prediction. For a threshold probability >50% (decision maker considers unnecessary surgery more regretful than failing to operate), the optimal decision is to follow the recommendations of the model. Specifically, for a threshold probability > 50% treatment should be administered if the probability of death as predicted by the model is greater than the threshold probability, and treatment should be held if the probability of death is less than the threshold probability. Conclusions: Regret theory in conjunction with regret based decision curve analysis provides a novel perspective in treatment decisions by incorporating the decision-maker's preferences with his/her estimates about benefits and harms of performing surgery.



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Post-radiation Metabolic Tumor Volume (MTV) and Survival in Esophageal Cancer A. Cruz,[1]* M. Chuong,[2] J. Weber,[2] E. Eikman,[2] H. Lomas,[1] J.M. Pimiento,[2] K. Almhanna,[2] R. Shridhar,[2] S.E. Hoffe,[2] K.L. Meredith.[2] *1. University of South Florida College of Medicine, Tampa, FL; 2. Moffitt Cancer Center, Tampa, FL.*

Introduction: PET-CT is an important tool for staging and evaluating treatment response in esophageal cancer. Metabolic tumor volume (MTV) has been reported as a prognostic factor in other malignancies. We evaluated the utility of post-radiation MTV in esophageal cancer patients treated with chemoradiotherapy (CRT). Methods: We evaluated pre-and post-treatment PET/CT scans in patients with squamous cell carcinoma (SCC) or adenocarcinoma (AC) treated with neoadjuvant/definitive intent. We measured the significance of the post-treatment MTV2.0-5.0 which was defined as the metabolic volume above a threshold SUV of x. Cox regression models were used to determine any significance between MTV2.0 -5.0 and disease free survival (DFS) or overall survival (OS). Multivariate analysis was performed. Results: We identified 63 patients (13 SCC, 50 AC) with a median follow-up of 12.0 months (range, 1.9-38.6). The median time to post-radiation PET/CT scan after completion of CRT was 40.1 days (range, 20-93). Thirty-seven (58.7%) patients underwent surgical resection. Univariate analysis revealed no significant correlation between post-treatment MTV and OS (MTV2.0 p = 0.968; MTV3.0 p = 0.945; MTV4.0 p = 0.890; MTV5.0 p = 0.316). There was also no significant correlation with respect to DFS (MTV2.0 p = 0.956; MTV3.0 p = 0.658; MTV4.0 p = 0.695; MTV5.0 p = 0.690). Multivariate analysis revealed that SCC histology and surgical resection were associated with improved OS while age, gender, post-radiation MTV2.0-5.0, and stage were not. Earlier stage and surgical resection were associated with improved DFS while post-radiation MTV2.0-5.0, age, gender, and histology were not. Conclusions: Although other studies have shown post-radiation MTV to be a significant prognostic factor, our data demonstrate no significant correlation with MTV and survival among esophageal cancer patients.

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What Provider Volume is Appropriate for Gastric Cancer Resection? Results of a RAND/UCLA Expert Panel M. Dixon,[1]* A. Mahar,[2] L. Paszat,[4] R. McLeod,[1] C. Law,[1] C. Swallow,[1] L. Helyer,[3] R. Seevaratnam,[1] R. Cardoso,[1] N. Coburn.[1] *1. Department of Surgery, University of Toronto, Toronto, ON, Canada; 2. Department of Community Health and Epidemiology, Queens University, Kingston, ON, Canada; 3. Department of Surgery, Dalhousie University, Halifax, NS, Canada; 4. Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada.*

Background: Some studies suggest an inverse relationship between volume and mortality. Optimal provider volumes for gastric cancer (GC) are unclear. Methods: A multi-disciplinary expert panel (16 physicians, 6 countries) scored 24 scenarios for appropriateness from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores (AS) from 1-3 were considered inappropriate, 4-6 uncertain, and 7-9, appropriate. Agreement was reached when 11 of 16 panelists scored the scenario similarly. If a scenario was

agreed to be appropriate, it was given a necessity score (NS) in the same manner. AS and NS are reported if agreement was met. Results: It is inappropriate for surgeons who perform <3 GC cases/yr to perform multi-visceral resections (MVR)(AS 1.0-1.5), D2 lymph node dissections (D2 LND)(AS 2.0), laparoscopic total gastrectomy (AS 2.0), or endoscopic mucosal resections (EMR)(AS 2.0). It is appropriate for a surgeon to have an annual volume of 11-20 cases/yr for open gastrectomy (AS 7.5-8.0) or a D2 LND (AS 7.0), and 20-50 cases/yr for MVR (AS 9.0), laparoscopic gastrectomy (AS 9.0), or EMR (AS 9.0). It is inappropriate for a hospital managing <5 cases/yr to perform D2 LND (AS 2.0), or laparoscopic total gastrectomy (AS 2.0). It is inappropriate for a hospital managing 11-20 cases/yr to perform an MVR involving a pancreaticoduodenectomy (MVR-PD)(AS 2.0), or EMR (AS 2.5). At least 21 cases/yr is an appropriate hospital volume for any GC procedure (AS 7.0-8.0). There was disagreement over the appropriateness of resection at hospitals with volumes of 5-20 cases/yr. It is inappropriate for an MVR to be performed in a hospital with no interventional radiology services (AS 2.5), and for an MVR-PD to be performed at a hospital with no level I intensive care unit (AS 1.0). Conclusions: The expert panel felt that resection of gastric cancer by extremely low volume providers was inappropriate for cases more complex than an open distal gastrectomy.

Table 1: Summary of inappropriate and appropriate surgeon and hospital volumes

Resection	Surgeon Volume		Hospital Volume	
	Inappropriate	Appropriate	Inappropriate	Appropriate
Open	N/A	≥ 11 cases/yr	N/A	≥ 21 cases/yr
Laparoscopic Total	< 3 cases/yr	≥ 20 cases/yr	< 5 cases/yr	≥ 21 cases/yr
Laparoscopic Distal	N/A	≥ 20 cases/yr	N/A	≥ 21 cases/yr
D2-LND	< 3 cases/yr	≥ 11 cases/yr	< 5 cases/yr	≥ 21 cases/yr
MVR	< 3 cases/yr	≥ 20 cases/yr	N/A	≥ 21 cases/yr
MVR-PD	< 6 cases/yr	≥ 20 cases/yr	< 10 cases/yr	≥ 21 cases/yr
EMR	< 6 cases/yr	≥ 20 cases/yr	< 10 cases/yr	≥ 21 cases/yr

N/A: appropriateness is indeterminant. D2 LND: D2 lymphadenectomy. MVR: multivisceral resection. MVR-PD: multivisceral resection involving a pancreaticoduodenectomy. EMR: endoscopic mucosal resection.

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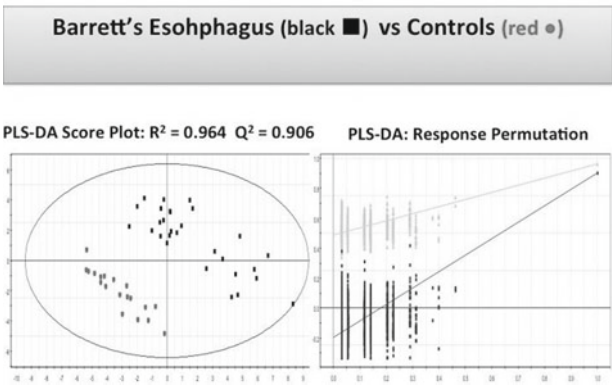
The Segregating Urinary Metabolomic Signature of Barrett's Esophagus V.W. Davis,* D.E. Schiler, M.B. Sawyer. *Resident, General Surgery, University of Alberta, Edmonton, AB, Canada.*

INTRODUCTION: Current screening and surveillance strategies for Barrett's esophagus are inadequate. More reliable tools are needed. A unique urinary metabolomic signature could fill this niche. We applied metabolomic techniques to identify urinary metabolites capable of facilitating in the diagnosis of Barrett's esophagus. METHODS: Urine samples from patients with histologically confirmed Barrett's esophagus (n=32) and normal, healthy volunteers (n=25) were collected and examined using 1H-NMR spectroscopy. Targeted profiling of spectra using Chenomx NMR Suite 7.0 software permitted the detection and quantification of 66 distinct metabolites. Unsupervised (principal component analysis, PCA) and supervised (partial-least squares discriminant analysis, PLS-DA) multivariate pattern recognition techniques were applied to discriminate between sample spectra of patients with Barrett's esophagus and healthy volunteers using SIMCA-P (version 11, Umetrics, Umeå, Sweden). RESULTS: Significant differences were found when comparing the concentrations of 59 metabolites in the urine of healthy volunteers and patients with Barrett's esophagus. Those metabolites contributing the most class discriminating information included 3-hydoxybutyrate, adipate and choline. Clear distinction between patients with Barrett's esophagus and healthy controls was noted when PLS-DA was applied to the data set (see Figure). Model parameters for both the goodness of fit R2, and the predictive capability Q2, were high (R2 = 0.96; Q2 = 0.90). Model validity was tested using response permutation and results were suggestive of excellent predictive power (see Figure). CONCLUSIONS: Urinary metabolomics identified a discrete signature associated with Barrett's esophagus compared to healthy controls. This profile has the potential to aid in diagnosis and the development of new therapeutic targets.



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65th SSO Annual Cancer Symposium

March 21-24, 2012
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65th Annual Cancer Symposium
Society of Surgical Oncology
March 21-24, 2012
Orlando, Florida

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