Abstract Book

Society of Surgical Oncology
66th Annual Cancer Symposium

National Harbor, Maryland
March 6-9, 2013

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

66th ANNUAL
Cancer
SYMPOSIUM
Society of Surgical Oncology
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ABSTRACTS

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Cytoreduction and HIPEC for Peritoneal Disease from Colorectal Carcinoma in The Netherlands: Long-term Outcome of Procedures Performed Under a Standardized Protocol A. Kuijpers,[1]* A. Aalbers,[1] S. Nienhuijs,[3] I. De Hingh,[3] R. Wiezer,[2] B. Van Ramshorst,[2] R. Van Ginkel,[4] K. Havenga,[4] A. Bremers,[6] L. Te Velde,[5] H. De Wilt,[6] V. Verwaal.[1] *1. Dutch Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 2. Sint Antonius Hospital, Nieuwegein, Netherlands; 3. Catharina Hospital, Eindhoven, Netherlands; 4. University Medical Centre Groningen, Groningen, Netherlands; 5. VU Medical Centre, Amsterdam, Netherlands; 6. University Medical Centre Nijmegen, Nijmegen, Netherlands.*

Question The HIPEC treatment for peritoneal surface malignancies from colorectal origin is now widely accepted worldwide. In the Netherlands, the treatment is only performed in dedicated centres that are trained by the first centre. The treatment protocol of all hospitals in the Netherlands as well as the data management is synchronized. In this study we assessed outcome in terms of disease-free survival and overall survival. Patients and methods The six hospitals of which patients were included, performed the treatment under a standardized protocol. Second procedures, open-close procedures and patients that underwent the HIPEC treatment for different pathology than colorectal malignancies were excluded from analysis. Disease-free survival was measured from the operation date to the date of recurrence. Overall survival was measured from date of surgery to date of death or last follow up. Survival was illustrated by Kaplan-Meier curves. Results From 1995-2012, 967 patients that underwent HIPEC treatment were included in this study. Sixty percent of the patients were female and 40% of the patients were male, with a median age of 58± 11.3 (range 21-81) years. Indications for CRS and HIPEC were peritonitis carcinomatosa (PC) from colorectal carcinoma in 69% of the cases and pseudomyxoma peritonei (PMP) in 31% of the cases. Median follow-up time was 41 months (range 0 to 186 months). Median progression-free survival was 34 months (95% confidence interval (CI) 30.5-37.5, Figure 1A). Median overall survival was 47 months (95% CI 39.4-54.6) (Figure 1A). Median survival for PC from colorectal carcinoma was 33 months (95% CI 28.4-37.6) and for PMP 115 months (95% CI 80.0-150.0, p<0.001, Figure 1C). Conclusions Cytoreduction and HIPEC showed a median overall survival of 47 months for all the metastatic colorectal and PMP patients that underwent this treatment in The Netherlands. This indicates that the protocol used in the Dutch hospitals is a well-established and safe protocol with good long-term results.

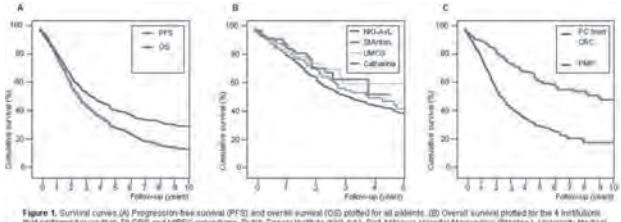

Figure 1. Survival curves (A) Progression-free survival (PFS) and overall survival (OS) plotted for all patients. (B) Overall survival plotted for the 4 institutions that performed more than 70 CRS and HIPEC procedures: Dutch Cancer Institute (NKI-AVL), Sint Antonius Hospital Nieuwegein (Martini), University Medical Centre Groningen (UMCG) and Catharina Hospital Eindhoven (Catharina). (C) Overall survival plotted for PMP and PC from colorectal carcinoma

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The 21-gene Recurrence Score (RS) Predicts Risk of Loco-regional Recurrence (LRR) in Node (+), ER (+) Breast Cancer (BC) after Adjuvant Chemotherapy and Tamoxifen: Results from NSABP B-28 E.P. Mamounas,[1]* G. Tang,[2] S. Paik,[3] F.L. Baehner,[4] Q. Liu,[2] J. Jeong,[2] S. Kim,[3] S.M. Butler,[4] F. Jamshidian,[4] D.B. Cherbavaz,[4] A.P. Sing,[4] S. Shak,[4] T.B. Julian,[5] B.C. Lembersky,[6] D.L. Wickerham,[5] J.P. Costantino,[2] N. Wolmark.[5] *1. NSABP Operations and Biostatistical Centers; Aultman Hospital, Canton, OH; 2. NSABP; University of Pittsburgh Graduate School of Public Health Department of Biostatistics, Pittsburgh, PA; 3. NSABP, Pittsburgh, PA; 4. Genomic Health, Inc, Redwood City, CA; 5. NSABP; Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA; 6. NSABP; University of Pittsburgh Cancer Institute, Pittsburgh, PA.*

BACKGROUND: RS predicts risk of distant recurrence in ER+ pts treated with adjuvant endocrine therapy. We evaluated the association between RS and risk of LRR in node (+), ER (+) patients (pts) treated with adjuvant chemotherapy plus tamoxifen in the NSABP B-28 trial. METHODS: B-28 compared doxorubicin/cyclophosphamide (AC X 4) vs. AC X 4 followed by paclitaxel X 4 in 3060 pts. Pts ≥50 yrs and those <50 yrs with ER+ and/or PR+ tumors also received tamoxifen. The present study includes 1065 ER+ pts, tamoxifen-treated, and with RS assessment. Lumpectomy pts received breast radiation (XRT). Mastectomy pts received no XRT. Sub-distribution analyses were used for LRR to account for competing risks, including distant recurrence, second primary cancers, and death due to other causes. RESULTS: Median follow-up was 11.2 yrs. There were 80 LRRs (7.5%) as first events (68% local/32% regional). RS was low in 36%, intermediate in 34% and high in 30%. RS was a significant predictor of LRR in univariate analyses (p<0.001, Table). RS was significantly associated with LRR after lumpectomy + breast XRT and after mastectomy (no XRT) as well as in pts with ≥4 + nodes (with a non-significant trend in pts with 1-3 + nodes, Table). In multivariate regression analysis adjusting for treatment and type of surgery, RS remained an independent predictor of LRR (HR: 2.61 [1.28-5.29] for a 50 point difference, P=0.008) along with pathologic nodal status (HR: 1.91 [1.20-3.03] for ≥4 vs. 1-3 positive nodes, P=0.007) and tumor size (HR: 1.28 [1.05-1.55] for a 1 cm difference, P=0.015). CONCLUSIONS: RS significantly predicts risk of LRR in node (+), ER (+) BC pts after adjuvant chemotherapy plus tamoxifen. These findings have clinical implications regarding selection of appropriate candidates for comprehensive XRT. Supported by: NCI grants U10-CA-12027, -69651, -37377, -69974, U24-CA-114732, and CA-75362, Susan G. Komen for the Cure® grants, and Bristol-Myers Squibb Pharmaceutical Research Institute

10-year Cumulative Incidence in Percentage (95% CI) of LRR According to the 21-Gene RS

Category	RS Low	RS Intermediate	RS High	Log-rank P-value
All patients (n=1065)	3.3 (1.8-5.5)	7.2 (4.8-10.3)	12.3 (8.9-16.2)	P<0.001
Lumpectomy + Breast XRT (n=461)	3.0 (1.1-6.4)	8.7 (5.0-13.6)	11.1 (6.2-17.6)	P=0.022
Mastectomy (n=604)	3.5 (1.5-6.8)	5.9 (3.1-10)	13 (8.7-18.1)	P=0.004
1-3 (+) Nodes (n=722)	3.2 (1.5-5.9)	5.1 (2.8-8.5)	7.9 (4.7-12.2)	P=0.12
≥4 (+) Nodes (n=343)	3.5 (1.1-8)	11.6 (6.5-18.4)	20.3 (13.3-28.4)	P=0.001

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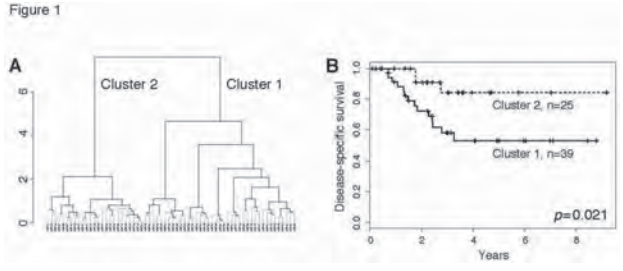
Genomic and Functional Analysis of Myxofibrosarcoma Identifies HGF/MET and Integrin α10 as Potential Prognostic Biomarkers and Novel Therapeutic Targets A.Y. Lee,* N.P. Agaram, L. Qin, A.M. Crago, R.B. O'Connor, N.D. Socci, T. Okada, S. Singer. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Myxofibrosarcoma (MXF) has few effective systemic therapies. We sought to identify genomic subtypes of MXF and to identify genes that associate with outcome and could serve as therapeutic targets. Methods: Gene expression was profiled in 64 untreated primary MXF samples using U133A arrays. Profiles were analyzed by unsupervised clustering and correlated with disease-specific survival (DSS). Differentially expressed genes between the two main clusters were screened for independent association with DSS and the most significant genes/pathways were functionally evaluated using shRNA knockdown and targeted drugs. Protein levels were assessed in preoperative serum by ELISA and in tumor tissue by immunohistochemistry. Results: Unsupervised clustering divided samples into 2 main clusters, which differed significantly in DSS (72% vs. 91% at 2 years; p=0.021; Fig. 1). Differentially expressed genes included ITGA10 (integrin α10) and MET (a receptor tyrosine kinase). Both were independently associated with DSS (HR=2.46 for ITGA10 and 7.25 for MET; both p<0.00005). Also associated with worse DSS were serum levels of HGF (the MET ligand) and HGF and MET staining in tissue. In 2 MXF cell lines with elevated MET the MET inhibitor PF2341066 blocked HGF-induced invasion. In an MXF cell line, but not in a normal adipose-derived stem cell line, ITGA10 knockdown decreased phospho-MET and phospho-AKT levels, eliminated proliferation and induced 12-17% apoptosis. Because SRC mediates integrin signaling, we tested the SRC inhibitor dasatinib on MXF cell lines with elevated ITGA10 or ITGA2 levels. Dasatinib decreased MET phosphorylation, inhibited proliferation by 66-100%, reduced migration by 48-59%, and reduced invasion by 66-90%. Conclusions: MXF is genomically complex and diverse, but gene expression profiles cluster tumors into two distinct genomic subtypes that differ in outcome. RNA levels of ITGA10, HGF and MET, serum HGF levels and tissue levels of MET

and HGF may be useful prognostic biomarkers in MXF patients. Drugs targeting ITGA10, MET and/or SRC may be active in this disease.

Figure 1



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Is Cancer Center Accreditation Associated with Improved Hospital Performance on Publicly Reported Quality Metrics? R.P. Merkow,[1]* J.W. Chung,[1] D.J. Bentrem,[1] J.L. Paruch,[2] K.Y. Bilimoria.[1] *1. Department of Surgery, Surgical Outcomes and Quality Improvement Center and the Northwestern Institute for Comparative Effectiveness Research (NICER) in Oncology, Northwestern University, Chicago, IL; 2. Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, IL.*

INTRODUCTION: Hospitals currently expend considerable effort and resources to earn and maintain Commission on Cancer (CoC) accreditation. However, it is unknown whether these hospitals offer better quality than non-CoC hospitals. As there are limited methods to study cancer quality at CoC vs. non-CoC hospitals, we sought to examine the effect of CoC accreditation on publicly reported quality metrics. METHODS: Data from Medicare's Hospital Compare and the American Hospital Association were merged. The association of CoC accreditation on patient safety indicators (PSI), Surgical Care Improvement Project (SCIP) processes of care, imaging efficiency and Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) measures were assessed with hierarchical regression methods. RESULTS: After excluding hospitals not providing any oncology related services, 2549 reported on PSIs (CoC: 44.2%), 2573 on SCIP (CoC: 43.8%), 2254 on imaging efficiency (CoC: 48.4%), and 2549 on HCHAPS (CoC: 44.2%) measures. For PSIs, no significant differences between CoC and non-CoC hospitals were observed for death, postoperative respiratory failure, venous thromboembolism (VTE) or wound dehiscence. Adherence on SCIP process of care measures was more likely at CoC hospitals for beta-blocker (OR 1.59, 95% CI 1.14-2.22), antibiotic (OR 1.79, 95% CI 1.37-2.33), and VTE (OR 1.96, 95% CI 1.33-2.86) indices. CoC hospitals were less likely to perform unnecessary double chest CT scans (OR 0.66, 95% CI 0.50-0.88), but not unnecessary abdominal CT or breast imaging. For HCAHPS, CoC accreditation was associated with worse overall satisfaction (OR 1.34, 95% CI 1.07-1.68), pain control (OR 1.28, 95% CI 1.01-1.61) and discharge instruction (OR 1.32, 95% CI 1.05-1.67) but not doctor communication (OR 0.87, 95% CI 0.70-1.10). CONCLUSION: Hospitals accredited by the CoC performed similar or better on many quality metrics. Although CoC accreditation may be a proxy which reflects a higher level of hospital commitment to overall quality improvement efforts, cancer patients and referring providers would likely benefit from public reporting of cancer-specific quality metrics.

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Intra-arterial Therapy for Advanced Intrahepatic Cholangiocarcinoma – A Multi-Institutional Analysis O. Hyder,[1] D. Cosgrove,[1] E. Liapi,[1] A. Zhu,[3] C. Sofocleous,[4] E. Petre,[4] D. Neal,[2] S. Kalva,[3] J.W. Marsh,[2] J. Geschwind,[1] T. Pawlik.[1]* *1. Surgery, Johns Hopkins University, Baltimore, MD; 2. University of Pittsburgh Medical Center, Pittsburgh, PA; 3. Massachusetts General Hospital, Boston, MA; 4. Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: Many patients with intrahepatic cholangiocarcinoma(ICC) present with advanced, inoperable disease. Traditionally these patients have been treated with systemic chemotherapy, however there is increasing interest in the use of loco-regional therapy. Data on the safety and efficacy of intra-arterial therapy(IAT) for ICC are, however, limited. Methods: Between 1993-2012, 153 patients with advanced ICC who were treated with IAT were identified from a multi-institutional database. Data on clinicopathological factors, morbidity, response rates using European Association for the Study of the Liver(EASL) criteria, as well as overall survival were collected and analyzed. Results: Median patient age was 61 years and the majority was female(54%). Median tumor size was 9.6 cm and 46% patients had a solitary lesion; 26% patients had extrahepatic disease and 11% had a prior surgical resection. 46% patients received systemic chemotherapy in addition to IAT. IAT consisted of standard transarterial chemoembolization (TACE)(84%), bland TAE(9%), or drug-eluting beads(DEB)(7%). Median number of IAT sessions was 2(range, 1-18). The median time between IAT sessions was 48 days. There were 18 peri-procedural complications for a morbidity of 12%; most complications were minor(n=13), however 5 patients had a grade 3-4 complication. Assessment of tumor response revealed complete or partial response in 24% patients, while 52% had stable disease. 24% of patients had intra-hepatic disease progression, while 20% had progression of extrahepatic disease. Median overall survival was 12 months and did not differ based on type of IAT (TACE, 12 mon vs. TAE 14 mon vs. DEB 10 mon; P=0.75). On multivariate analysis, increasing number of IAT sessions (HR 0.90, 95% CI 0.84-0.95) and IAT response (HR complete-partial response, 0.50 95% CI 03.0-0.85) were associated with better survival(both P<0.05). Conclusions: IAT for ICC was safe and provided good loco-regional control of disease in up to three-quarters of patients. Among patients with an IAT response, overall survival was prolonged. The role of IAT therapy for ICC warrants further prospective evaluation in clinical trials.

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How Often is Axillary Dissection Avoided when Z11 Eligibility Criteria are Applied in Routine Practice: Results From a Prospective Series of Consecutively Treated Patients L.T. Dengel,* M.J. Junqueira, K.J. Van Zee, T.A. King, H.S. Cody, M. Stempel, D. Capko, M. El-Tamer, M.L. Gemignani, A. Heerdt, G. Plitas, V. Sacchini, L.M. Sclafani, S. Patil, M. Morrow. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction The ACOSOG Z11 trial demonstrated no benefit in survival or local control for T1-2 patients with 1-2 positive sentinel nodes (SN) undergoing breast conservation (BCS) with SN biopsy alone compared with completion axillary dissection (ALND). There are concerns that trial patients were low risk and that results may not be applicable to the broader population, particularly young women and those with hormone receptor (HR) negative cancer. Here we prospectively assess the applicability of Z11 in a cohort of consecutive patients. Methods In 8/2010 an institutional treatment algorithm based on Z11 eligibility criteria was prospectively applied to consecutive patients having BCS. Patients with and without indications for ALND were compared using Fisher's exact and Wilcoxon rank sum tests. Results From 8/2010-7/2012, 1860 invasive breast cancer patients had BCS; 341 had nodal metastasis and 88 did not meet Z11 criteria. Of 253 with ≥1H&E-positive SN on routine section, 212 (84%) had indications for SN only. ALND was indicated in 41 for ≥3 +SNs(n=31,12%) or extracapsular extension (n=10,4%). An additional 4 patients had ALND for patient/MD preference and were analyzed with the SN group. The median number of SNs was 3 in the SN group vs 5 in the ALND group (p<.0001). Characteristics of the groups are compared in the Table. Age, HR, HER2, and grade did not differ; as expected, tumors were larger in the ALND group (p<0.0001). Using the MSKCC nomogram, the median likelihood of additional positive nodes in the SN group was 33% (5-81%), similar to Z11, vs 58% (6-94%) in the ALND group (p<0.0001). 34 of 41 patients had the indicated ALND, and 74% had more positive nodes (median=3;1-19). No axillary recurrences have occurred at a median follow-up of 11 months. Conclusions Our consecutive series of BCS patients had characteristics very similar to patients in Z11, and ALND was avoided in 84%. Age, HR, and HER2 were not predictive of a tumor burden requiring ALND, suggesting that they should not be used as selection criteria. Longer follow-up is needed to assess the incidence of axillary recurrence.

Table 1. Characteristics of SN and ALND patients.

	SN (212)		ALND (41)		p-value
Age	median	min, max	median	min,max	
	58	28, 92	60	35, 82	0.74
	n	%	n	%	
Pathology T Size					
≤ 2cm (T1)	150	70.8%	17	41.5%	
> 2cm (T2, T3)	62	29.2%	24	58.5%	<0.0001
Subtype*					
HR+/HER2-	179	84.4%	32	80.0%	
HR+/HER2+	14	6.6%	2	5.0%	
HR-	19	9.0%	6	15.0%	0.43
Histologic grade					
1 (includes lobular)	21	9.9%	8	19.5%	
2	48	22.6%	7	17.1%	
3	143	67.5%	26	63.4%	0.18

*1 tumor in the ALND group was too small for HER2 testing.
SN, sentinel node; ALND, axillary lymph node dissection; HR, hormone receptor

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Invasive Carcinoma in Intraductal Papillary Mucinous Neoplasms of the Pancreas can be Predicted with a Nomogram C. Correa,* R. Do, M. Gonen, J. Lafemina, M. D'Angelica, R.P. DeMatteo, Y. Fong, T. Kingham, M.F. Brennan, W.R. Jarnagin, P.J. Allen. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Background Preoperative identification of patients at high risk for harboring carcinoma in intraductal papillary mucinous neoplasms (IPMN) remains a challenging task. Even with strict criteria, the majority of resected lesions lack high-grade dysplasia or invasive carcinoma on final pathologic examination. Methods We evaluated all patients who have undergone resection for histologically confirmed IPMN who had preoperative imaging available for review. Three blinded hepatobiliary radiologists independently reviewed preoperative imaging and recorded cyst characteristics including diameter, presence of solid component, and subtype; mixed-type IPMNs were grouped with main-duct lesions for this analysis. Using an ordinal logistic regression model including demographic, perioperative, and radiologic characteristics, we devised two independent nomograms to predict ordinal progression from adenoma, to high-grade dysplasia/carcinoma in situ (HGD-CIS), and invasive carcinoma in both main and branch-duct IPMN. Bootstrap validation was used to evaluate the performance of these models and a concordance index was derived from this internal validation. Results Two-hundred and nineteen patients who met criteria for this study were identified. Branch-duct IPMN (bdIPMN) comprised 56 % of the resected lesions. The proportion of HGD-CIS was 15% for bdIPMN and 33% for mdIPMN (P: 0.003). Invasive carcinoma was identified in 15% of bdIPMN and 41% of main-duct lesions (P< 0.001). On multivariate regression, patient gender, history of prior malignancy, presence of solid component and weight loss were found to be significantly associated with the ordinal outcome for patients with mdIPMN and built into the nomogram; the concordance index for this model was 0.74. For patients with bdIPMN, weight loss, solid component, and maximum lesion diameter were associated with the outcome; this model displayed a concordance index of 0.74. Figure. Conclusion This study developed two nomograms that can be used to predict a patient's individual likelihood of harboring high-grade dysplasia or invasive malignancy in a radiologically diagnosed IPMN. External validation is ongoing.

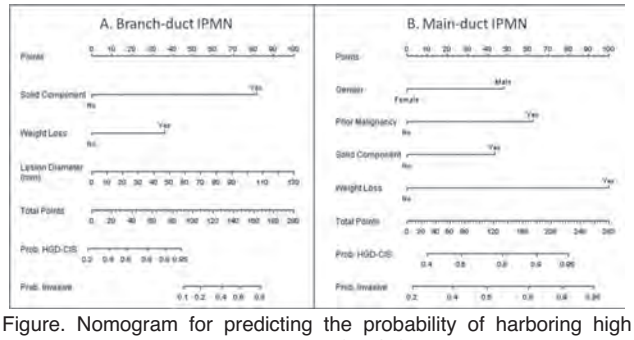

Figure. Nomogram for predicting the probability of harboring high grade dysplasia/carcinoma in situ (HGD-CIS) or Invasive malignancy in branch-duct (A) and main-duct IPMN (B).

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Recurrence Score Along the Continuum of Increasing Nodal Burden in Breast Cancer F. Smith,* M.C. Lee, G. Acs, W. Fulp, J. Lee, N. Khakpour, J.V. Kiluk, C. Laronga. *H Lee Moffit Cancer Center, Tampa, FL.*

Introduction: The Oncotype Dx (ODX) Recurrence Score (RS) stratifies breast cancer patients (pts) by risk of recurrence and potential benefit of adjuvant chemotherapy. Pts with early stage, estrogen receptor (ER) positive, lymph node-negative breast cancer were included in the initial validation studies. Limited data exists on the application of ODX in node positive pts. We review our experience with RS along the continuum of nodal burden. Methods: A prospective database of pts with breast cancer for whom ODX RS was obtained for treatment planning was reviewed by final surgical pathology. Patients were grouped into 4 pathological categories: negative sentinel lymph node [N0(i-)], isolated tumor cells [N0(i+)], micro-metastasis [N1mic] and macro-macrometastasis [N1, 1-3 + nodes]. P values were calculated using the exact Wilcoxon Rank Sum Test. Results: 637 pts were identified in the study period: 521 (81.8%) pts had negative sentinel lymph nodes; 54 (8.5%) pts had isolated tumor cells (N0(i+)); 29 (4.6%) pts had N1mic, and 33 (5.2%) had N1 disease (Table). Median age overall was 58yrs, median invasive tumor size was 1.5cm; 475 (91.2%) had ductal histology. Median RS for the study pts was 17 (range 0-85), and increasing RS had no correlation to increasing nodal burden (p=0.23). Pathologic factors associated with nodal status were lymphovascular invasion (LVI) and histology. The frequency of LVI was higher with increasing nodal burden (p<0.0001). Ductal histology was significantly associated with abnormal nodal findings. (p = 0.002). Age, mitotic rate, grade and degree of ER positive staining on IHC were not significantly associated with sentinel lymph node status (p > 0.05). Conclusion: Tumor size, histology and LVI were significant predictors of increased nodal burden. However, ODX RS was neither predictive nor reflective of increasing nodal disease. RS is a potentially useful tool in adjuvant systemic treatment decisions in patients with positive lymph nodes but should not impact decisions regarding local-regional therapy.

Table 1.

	N(n=521)	N0 i+ (n=54)	N1 mi (n=29)	N1 (n=33)	P value
Median Age (yrs)	58	57.5	59	55	0.56
Median tumor size (cm)	1.5	1.7	1.6	1.9	0.002
LVI present (%)	40 (7.7)	11 (20.4)	7 (24.1)	11 (33.3)	< 0.0001
Median ODX RS	17	15	15	14	0.49

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Factors Affecting Sentinel Lymph Node Identification Rate after Neoadjuvant Chemotherapy for Breast Cancer Patients Enrolled in ACOSOG Z1071 J.C. Boughey,[1]* V.J. Suman,[1] E.A. Mittendorf,[2] G.M. Ahrendt,[3] L.G. Wilke,[4] B. Taback,[5] A. Leitch,[6] T.S. Flippo-Morton,[7] D.R. Byrd,[8] D.W. Ollila,[9] T.B. Julian,[10] S.A. McLaughlin,[11] K. Hunt.[2] *1. Surgery, Mayo Clinic, Rochester, MN; 2. MD Anderson Cancer Center, Houston, TX; 3. Magee-Womens Surgical Associates, Pittsburgh, PA; 4. University of Wisconsin-Madison, Madison, WI; 5. Columbia University Medical Center, New York, NY; 6. University of Texas Southwestern Medical Center, Dallas, TX; 7. Carolinas Medical Center, Charlotte, NC; 8. University of Washington Medical Center, Seattle, WA; 9. University of North Carolina - Chapel Hill, Chapel Hill, NC; 10. Allegheny General Hospitall, Pittsburgh, PA; 11. Mayo Clinic, Jacksonville, FL.*

Background: Sentinel lymph node (SLN) surgery is increasingly used for nodal staging in patients receiving neoadjuvant chemotherapy (NAC). Patients enrolled on the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial were node positive at presentation and underwent both SLN surgery and axillary lymph node dissection (ALND) after completion of NAC. Herein we evaluate the factors affecting the SLN identification rate. Methods: ACOSOG Z1071 was a prospective clinical trial enrolling women with clinical T0-4, N1-2, M0 breast cancer receiving NAC. At surgery after chemotherapy, all patients were to undergo SLN surgery and planned completion ALND. Patient and disease characteristics as well as SLN mapping technique were examined for their impact on the failure to identify a SLN. Results: A total of 756 patients were enrolled from July 2009 to July 2011. Fifteen women were ineligible, 34 withdrew and 12 underwent ALND only. 695 women had SLN surgery attempted, of which 2 did not undergo ALND. At least one SLN was identified in 645 patients (92.8%). Univariate analysis found failure to iden-

tify a SLN differed with respect to type of tracer used. Failure to identify a SLN was highest when blue dye alone was used (20.7%). The SLN failure rate was 8.7% with use of radiolabelled colloid alone and 6.2% with dual tracer. Patient factors (age, BMI), tumor factors (clinical T stage, clinical N stage) and nodal response to chemotherapy did not significantly affect the SLN identification rate. Site of tracer injection, length of chemotherapy treatment and year of surgery also did not impact identification rate (see Table). Multivariate analysis found that mapping with blue dye alone increases the likelihood of not identifying the SLN relative to using radiolabelled colloid or both (p=0.007; OR=3.69 95%CI: 1.43-9.53). Conclusions: SLN identification rate after completion of NAC is higher with use of radiolabelled colloid or dual tracer technique. No other factors significantly impacted SLN identification. Optimal tracer use is important to ensure success in performing SLN surgery after NAC.

Factors associated with failure to identify a SLN

Variable		Failure to identify a SLN (%)	Odds Ratio (95% CI)	P value
Number of Tracers	Single tracer (blue dye or radiolabeled colloid)	16/145 (11.0%)	1	0.047
	Dual tracers (blue dye and radiolabeled colloid)	34/550 (6.2%)	0.53 (0.28-0.99)	
Type of Tracer	Radiolabeled colloid	10/116 (8.6%)	1	0.005
	Blue dye	6/29 (20.7%)	3.96 (1.51-10.4)	0.339
	Both	34/550 (6.2%)	1.43 (0.69-2.99)	
Clinical T stage at presentation	Tis/T0/T1	7/97 (7.2%)	1	0.647
	T2	23/382 (6.0%)	0.82 (0.34-1.96)	0.569
	T3/4	20/216 (9.3%)	1.30 (0.53-3.18)	
Clinical N stage at presentation	N1	46/656 (7.0%)	1	0.450
	N2	4/39 (10.3%)	1.51 (0.52-4.45)	
Final pathologic nodal status	Negative	24/282 (8.5%)	1	0.276
	Positive	26/411 (6.3%)	0.73 (0.41-1.29)	
Site of tracer injection	Multiple	10/146 (6.8%)	1	0.740
	Subareolar	27/444 (6.1%)	0.88 (0.42-1.87)	0.112
	Peri-tumoral	8/57 (14.0%)	2.22 (0.83-5.95)	0.565
	Intradermal	2/19 (10.5%)	1.60 (0.32-7.92)	------
	Unknown	3/29 (10.3%)	--------	
BMI	BMI < 25.0 (underweight/normal)	10/195 (5.1%)	1	0.186
	BMI ≥ 25.0 (overweight/obese)	40/497 (8.0%)	1.62 (0.79-3.31)	------
	unknown	0/3 (0%)	------	
Patient age	Age ≤ 50 yrs.	21/346 (6.1%)	0.71 (0.40-1.28)	0.255
	Age > 50 yrs.	29/349 (8.3%)	1	
Length of chemo	≤ 90 days	3/60 (5%)	1	0.737
	91-135 days	22/360 (6.1%)	1.24 (0.36-4.27)	0.304
	136 + days	25/274 (9.1%)	1.91 (0.56-6.54)	------
	unknown	0/1 (0%)	------	
Year of surgery	2009-2010	29/370 (7.8%)	1.23 (0.69-2.20)	0.484
	2011-2012	21/325 (6.5%)	1	

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Outcomes after Mastectomy for Node-positive Breast Cancer: Comparison of Women Treated With and Without Completion Axillary Dissection at NCCN Cancer Centers R.A. Greenup,[1]* T. Breslin,[2] S.B. Edge,[3] M.E. Hughes,[4] E.S. Hwang,[1] C. Laronga,[5] P. Marcom,[1] B. Moy,[6] R.A. Otteson,[7] H. Rugo,[8] J.L. Wilson,[9] Y. Wong,[10] J.C. Weeks.[4] *1. Duke University Medical Center, Durham, NC; 2. University of Michigan, Ann Arbor, MI; 3. Roswell Park Cancer Institute, Buffalo, NY; 4. Dana Farber Cancer Institute, Boston, MA; 5. Moffitt Cancer Center, Tampa, FL; 6. Massachusetts General Hospital, Boston, MA; 7. City of Hope National Medical Center, Duarte, CA; 8. UCSF, San Francisco, CA; 9. Ohio State University Medical Center, Columbus, OH; 10. Fox Chase Cancer Center, Philadelphia, PA.*

Background: The results of ACOSOG-Z0011 changed the management of patients with sentinel lymph node positive breast cancer undergoing breast conservation therapy (BCT). Limited data exists on outcomes of women with node-positive early-stage breast cancer treated with mastectomy without completion axillary lymph node dissection (ALND). We compared recurrence and survival among women with node-positive T1 or T2 breast cancers treated with mastectomy with or without ALND. Methods: 11,211 women with clinical T1/T2, N0 breast cancer who underwent definitive breast and axillary surgery from July 1, 1997 to December 31, 2007 were identified in the NCCN Breast Outcomes Database. Prospectively gathered data were evaluated for patient and tumor characteristics, year of diagnosis, recurrence and survival. Surgical management of the axilla (sentinel lymph node biopsy (SLNB) +/- ALND) was evaluated. Cox regression analysis was used to compare overall survival, adjusting for age, stage, and type of axillary surgery. Results: 2,345 patients with a positive sentinel lymph node were identified; 307(13%) underwent SLNB without ALND, and 2,038(87%) underwent completion ALND. 998 women underwent mastectomy, with 79(8%) of this cohort undergoing SLNB alone [N1mic: 42(53%); N1: 31(39%); N2/N3: 2(3%)]. At a median follow-up of 5.2 years, there were 12 local recurrences among women who had mastectomy, one after SLNB alone and 11 following SLNB+ALND. Adjusted overall survival was significantly associated with age at diagnosis, nodal tumor burden, and T stage. However, ALND did not confer a significant survival advantage among women undergoing mastectomy (adjusted HR 0.65, 95% CI 0.32-1.32) or BCT (adjusted HR 0.73, 95% CI 0.48-1.11). Conclusions: In a population of predominantly N1mic and N1 patients with early stage breast cancer treated with mastectomy, extent of axillary surgery was not independently associated with overall survival. These data suggest that in node-positive patients undergoing mastectomy selective use of SLNB alone may be used without compromising outcome.

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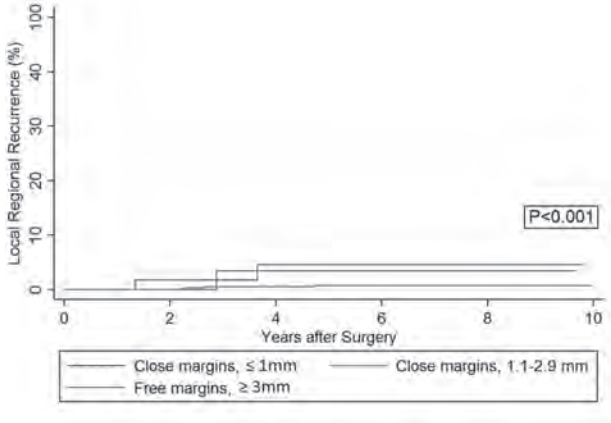
Incidence and Consequence of Close Margins for Ductal Carcinoma In Situ Treated with Mastectomy E. FitzSullivan,* S.A. Lari, B. Smith, A.S. Caudle, S. Krishnamurthy, A. Lucci, E.A. Mittendorf, G. Babiera, S. Black, J.L. Wagner, I. Bedrosian, W. Woodward, S.M. Gainer, R. Hwang, F. Meric-Bernstam, K. Hunt, H.M. Kuerer. *UT MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: The impact of close or positive margins for DCIS treated with mastectomy is unclear and may lead to post-mastectomy radiotherapy (PMRT). This study is the largest reported cohort of women with DCIS treated with mastectomy examining the incidence and clinical consequence of close margins. METHODS: From 1996 to 2009, 810 patients with DCIS were treated with mastectomy. Final width of histologic margin was evaluated and free margins were defined as ≥3 mm (n=716). Clinical and pathologic factors were compared and analyzed. Median follow-up was 6.3 years. RESULTS: Overall, close or positive margins occurred in 11.7% of patients (positive, n=4; ≤ 1 mm, n=59; 1.1-2.9 mm, n=35). Independent risk factors for close or positive margins included: multicentric disease (odds ratio [OR] = 5.4), pathologic size ≥ 1.5 cm (OR = 5.1), and presence of necrosis (OR = 2.5), but not age, skin-sparing mastectomy, or immediate reconstruction (P>0.05). Seven patients (0.9%) received PMRT for positive or close margins and none of these patients had a local regional recurrence (LRR). Among the remaining 803 patients that did not receive PMRT, the 10-year LRR rate for the entire group was 1%, 5.0% for margin ≤ 1 mm, 3.6% for margin 1.1-2.9 mm, and 0.7% for free margins(P<0.001; Figure). No difference in LRR was seen with ≤ 1 mm vs. 1.1-2.9 mm margins (P=0.57). The 10-year rate of contralateral breast cancer development was 6.4%. Using multivariate cox proportional hazard analysis, close margins was the only independent predictor of LRR (Hazard Ratio = 8.4, P =0.005). CONCLUSIONS: Close margins occur in a minority of patients undergoing mastectomy for DCIS and is the only independent risk factor for LRR. However, given the low LRR rate for DCIS treated with mastectomy with close margins, which is less than the rate of contralateral breast cancer development, PMRT should be reserved for patients with multiple close/positive margins that cannot be surgically excised.



Local Regional Recurrence Rate After Mastectomy for DCIS

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Margins in Breast Cancer Surgery: How Close is Too Close?
E.M. Garvey,* D. Senior, B.A. Pockaj, N. Wasif, A.C. Dueck, A.E. McCullough, I.T. Ocal, R. Gray. *The Mayo Clinic Arizona, Phoenix, AZ.*

INTRODUCTION: There is no consensus on the width of tissue margin that should prompt re-excision surgery for breast cancer. METHODS: A prospective database at a single institution was reviewed from 2000-2012. Institutional protocol is to perform re-excision surgery when margins are <2 mm. RESULTS: There were 2,520 procedures; 63% of patients underwent lumpectomy. Re-excision surgery was performed for 12% of lumpectomy patients including 10% who completed breast conserving therapy (BCT) and 2% who ultimately underwent mastectomy. Residual disease was present in 38% of these patients. Among up-front mastectomy patients, 2% underwent re-excision surgery and 26% had residual disease. Among those with residual disease, 74% had only DCIS remaining. The rates of residual disease for patients with positive, 0.1-0.9 mm, and 1.0-1.9 mm margins were 40%, 38%, and 33% respectively. Age, race, menopause status, width of closest final margin, tumor histology, hormone receptor status, triple-negative disease, and presence of angiolymphatic invasion were not significantly associated with residual disease being present on re-excision. The presence of multiple margins <2 mm trended toward significance (p = 0.06). Median follow-up was 43 months (range 0-140 months). The five-year local recurrence (5-yr. LR) rates were 1.9% for BCT patients and 1.1% for mastectomy patients. The 5-yr. LR rates were 1.8% for BCT patients not undergoing re-excision, 4.3% for BCT patients undergoing re-excision with completion of BCT, and 0% for BCT patients converted to mastectomy. The hazard ratio (HR) for LR trended higher for BCT patients who underwent re-excision [HR=2.15, 95% confidence interval (CI)=0.87-5.31, p=0.09] and reached statistical significance when patients converted from BCT to mastectomy were excluded (HR=2.56, 95% CI=1.04-6.32, p=0.04). CONCLUSIONS: Breast cancer patients with margins of excision narrower than 2 mm have a substantial risk of residual disease, and no clinical scenario could be identified with negligible risk. A policy of re-excision of any margin closer than 2 mm can produce excellent 5-yr. LR rates, although patients requiring re-excision who complete BCT have a higher risk of local recurrence.

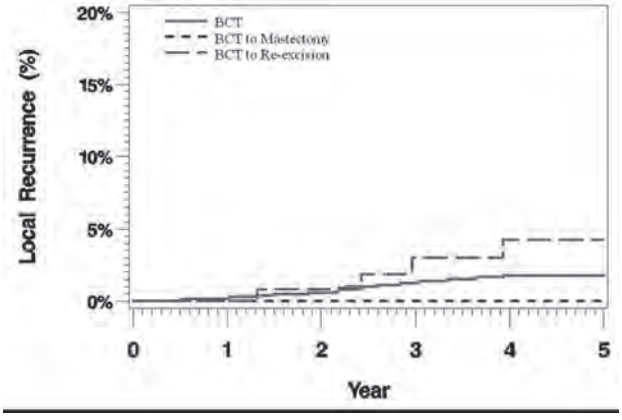

Figure 1. Kaplan-Meier plot of time to local recurrence for breast conserving therapy not undergoing re-excision (BCT), BCT converted to mastectomy (BCT to Mastectomy) and BCT undergoing re-excision (BCT to Re-excision)

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Contralateral Prophylactic Mastectomy for Unilateral Breast Cancer: A Review of the National Comprehensive Cancer Network (NCCN) Database
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Background. A progressive increase in the use of contralateral prophylactic mastectomy (CPM) for the treatment of unilateral breast cancer (UBC) has been observed over the last decade. Prior research has provided inconsistent results about the effect of CPM on survival. NCCN data was used to characterize temporal trends, demographic/clinical characteristics, and the survival effects of CPM. Methods. We evaluated the use of CPM within one year of unilateral mastectomy (ULM) among 8,353 patients (pts) diagnosed with DCIS and Stage I-III UBC from 1998-2007 who underwent ULM at 13 NCCN institutions. Factors associated with CPM were assessed using multivariable logistic regression, separately for the DCIS and invasive pts controlling for year of diagnosis, institution, pathology, and treatment. Cox regression was used for survival analyses. Results. 21% (273/1,309) of pts with DCIS and 17% (1,199/7,044) with Stage I-III disease underwent CPM within one year of ULM. CPM increased over time (1998-2007), from 15% to 27% (p=.12) in DCIS pts and from 8% to 26% in cancer pts (p<0.0001). Pts who were younger and Caucasian were more likely to undergo CPM (p<.0001 for DCIS; p<.0001 for stage I-III). Stage I-III pts with education beyond high school were also more likely to undergo CPM (OR 1.3, 95% CI: 1.0-1.5). DCIS pts with tumors <1 cm were more likely to have CPM (OR 1.9, 95% CI: 1.2-2.9) while stage I-III pts with node negative disease were more likely to get CPM than those with >4 positive nodes (OR 1.5, 95% CI: 1.2-1.9). There was wide institutional variation in CPM usage (8.2%-34.7% for DCIS and 3.6%-30.8% for stage I-III pts). Among pts with median follow-up of 4.5 years, there was no difference in overall survival between ULM alone vs. ULM+CPM, after controlling for demographic, clinical and treatment factors. Conclusions. The NCCN experience documents the increasing trend of CPM in UBC pts. CPM was more common among women with better prognosis primary tumors and those who were younger, Caucasian, and more highly educated. Controlling for demographic and clinical characteristics, there was no survival advantage for CPM.

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Operative Risks Associated with Contralateral Prophylactic Mastectomy: A Single Institution's Experience
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Introduction: The rates of contralateral prophylactic mastectomy (CPM) have risen dramatically over the past decade, yet the risks of CPM have not been well delineated. We hypothesized that operative risks of CPM would be greater than those of unilateral mastectomy (UM). Methods: 544 patients underwent either UM or CPM between January 2009 and March 2012 for unilateral breast cancer. Operative complications were classified as minor (aspirations, infections, partial necrosis, minor bleeding) or major (hematoma or seroma requiring operation, infection requiring rehospitalization, blood product transfusion, total flap or nipple loss). Chi square and multivariate logistic regression were used for the analysis. Results: The mean age of the cohort was 57 years old and 346 (64%) were UM and 198 (36%) CPM. Of the 371 (68%) patients who underwent reconstruction, 124 (33%) were autologous reconstruction. There were 343 (63%) smokers and 61 (11%) diabetics. The overall complication rate in the CPM group was significantly higher than the UM group (43% vs 30%, p=0.001). Minor complications were significantly greater in the CPM vs UM group (34% vs 24%, p=0.001) but major complications (14% vs 12%) and number of complications (14% vs 17%) were not significantly different. When age, body mass index, smoking and diabetes history, AJCC stage, reconstruction, and previous radiation therapy were adjusted for, CPM patients were 47% more likely to have any complication compared to UM patients (OR 1.47, 95% CI 0.996-2.169, p=0.05). Other significant fac-

tors associated with any complication in the multivariate model were reconstruction (OR 1.96, 95% CI 1.24-3.10) and smoking history (OR 1.58 95% CI 1.09-2.30). When minor complications were examined adjusting for the aforementioned factors, CPM patients were 45% more likely to have a minor complication (OR 1.45, 95% CI 0.964-2.185, p=0.075) than UM patients. Conclusions: CPM is associated with more overall complications compared to UM but these are mainly minor complications. This data may inform patient and physician decisions to choose CPM.

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RET Inhibitor Combined with Anti-Estrogen Therapy Offers a New Treatment Strategy for Breast Cancer P.M. Spanheimer,* A.R. Cyr, J.C. Carr, M.P. Gillum, M.V. Kulak, G.W. Woodfield, S.L. Sugg, R.J. Weigel. *Surgery, University of Iowa, Iowa City, IA.*

Background: The RET proto-oncogene is expressed in breast cancer in association with the estrogen receptor (ER). Activation of RET by glial cell line derived neurotropic factor (GDNF) leads to activation of ERK1/2 and proliferation. We investigated the effects of sunitinib, a small molecule Ret inhibitor in breast cancer. Methods: S phase, Ki-67 proliferative index and cleaved caspase 3 (CC3) apoptotic marker were analyzed in MCF-7 ER+ breast cancer cells using fluorescence activated cell sorting (FACS). Mice with MCF-7 xenografts were given daily oral gavage with sunitinib 40 mg/kg/day. Fresh human primary breast tumor tissue was treated in vitro with GDNF and analyzed for RET expression and the effect of sunitinib on ERK1/2 activation. Results: Treatment of MCF-7 cells with sunitinib reduced proliferation, S phase, and Ki-67 induction by GDNF and increased CC3, p=0.02 (Figure 1A, 1B). Treatment with both sunitinib and tamoxifen demonstrated additive effects to decrease proliferation (p<0.001), S phase (p=0.007), and Ki-67 (p=0.01), and induce CC3 (p=0.001). Athymic mice treated with sunitinib had reduced MCF-7 xenograft formation at three weeks compared to control mice, (33% vs 100%, p=0.05), Figure 1C. In 12 primary human tumor tissue samples mean expression of the Ret receptor in ER+ tumors was 14 fold higher compared to ER- tumors (p=0.04), and 20 fold higher than patient matched normal breast tissue (p=0.02), Figure 1D. Treatment with sunitinib resulted in a mean decrease in ERK1/2 activation of 38% in all tumors (p<0.001) with a 2.7 fold larger reduction in ER+ tumors, p=0.02 (ER+ 52%, p<0.001 vs. ER- 19%, p=0.03), Figure 1E. Conclusions: Sunitinib significantly reduced proliferation and induced apoptosis in MCF-7 cells with effects that were additive with tamoxifen. In pre-clinical animal studies, sunitinib treatment significantly reduced MCF-7 xenograft tumorigenesis. Furthermore, sunitinib inhibited ERK1/2 activation in primary human breast cancers with more pronounced effects in ER+ tumors. Together, these results indicate that combination therapy with anti-estrogens and a RET inhibitor may offer a novel treatment strategy in breast cancer.

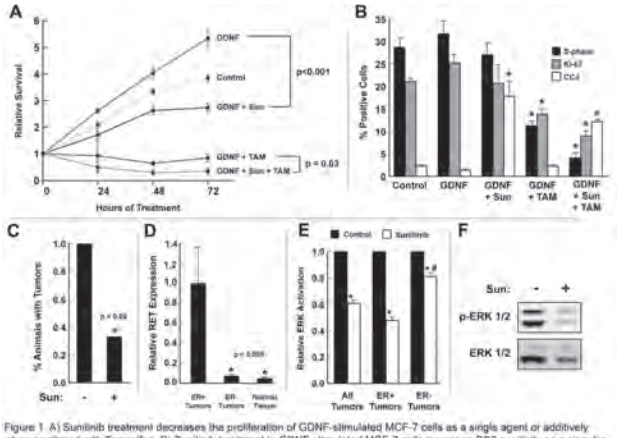

Figure 1 A) Sunitinib treatment decreases the proliferation of GDNF-stimulated MCF-7 cells as a single agent or additively when combined with Tamoxifen. B) Sunitinib treatment in GDNF-stimulated MCF-7 cells increases CC3 positivity as a singular agent and works additively with Tamoxifen to reduce the percentage of cells that are in S-phase and stain positive for Ki-67. *p<0.05 compared to GDNF treatment alone. C) Sunitinib treatment significantly reduced the incidence of tumor development in an MCF-7 xenograft tumorigenesis model. D) RET expression is significantly higher in ER-positive primary human breast tumors compared with ER-negative and normal breast tissue. E) Sunitinib treatment significantly reduced levels of ERK1/2 activation in all primary tumors evaluated. This effect was more pronounced in ER-positive tumors. *p<0.05 compared to paired control; # p<0.05 compared to ER-positive sunitinib treatment group. F) Representative western blot for evaluating ERK1/2 activation in primary human breast tumors.

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Peritumoral Expression of Adipokines and Fatty Acids in Breast Cancer J.L. Gnerlich,[1]* K. Yao,[2] A.M. Wyrwicz,[2] P. Fitchev,[3] S.E. Crawford.[3] *1. University of Chicago Medical Center, Chicago, IL; 2. NorthShore University HealthSystem, Evanston, IL; 3. Saint Louis University, Saint Louis, MO.*

Background: We hypothesized that peri-tumoral fat can be a rich source of lipid-derived energy for tumors by increasing adipose triglyceride lipase (ATGL)-mediated TAG catabolism, release of fatty acids and downregulating a negative regulator of adipogenesis, pigment epithelium-derived factor (PEDF). Methods: Fresh adipose tissue from therapeutic (n=17) and prophylactic mastectomy (n=3) specimens was harvested peritumoral and compared to adipose tissue distant for pigment epithelium derived factor (PEDF), (ATGL) and leptin using immunohistochemistry. High resolution 1H MR spectra of the specimens were acquired on a 600MHz MR spectrometer and relative amounts of mono-unsaturated (fmono), poly-unsaturated (fpoly) and saturated fatty acids (fsat) were calculated. Results: Mean tumor size was 2.3cm and 10 (59%) patients had tumor positive nodes. Mean BMI was 27.9kg/m2. Peritumoral PEDF and the leptin/PEDF ratio expression was significantly affected by node status and tumor size. Expression of PEDF was significantly decreased (n=8) in the peritumoral stroma of node positive cases versus node negative cases (n=9; mean =1.22 +/- 0.15 vs. 1.88 +/- 0.23, p<0.05). The leptin/PEDF ratio was markedly elevated in the peritumoral region node positive cases compared to node negative cases (mean = 2.17+/-0.17 vs. 1.23 +/- 0.15, p<0.001). Tumors >2cm had lower peritumoral stromal expression of PEDF than tumors <2cm (p=0.01). In all fat tissue derived from obese patients (BMI >30kg/m2), ATGL expression was significantly increased compared to the non-obese group (BMI<30kg/m2) (p<0.05) but peritumoral expression was not significantly altered. 1H MR spectroscopy revealed the ratio of fmono/fsat was elevated in the peritumoral breast tissue (2.17) relative to tissue located away from the cancer (1.12). The ratio fpoly/fsat was similar. Conclusions: Peritumoral expression of adipokines is altered by tumor factors suggesting a role for adipokines in enhancing tumor growth in the adipocyte-rich environment. MR spectroscopic evaluation of fatty acid composition might be a useful tool in characterizing the metabolic alterations in the tumor microenvironment in breast cancer.

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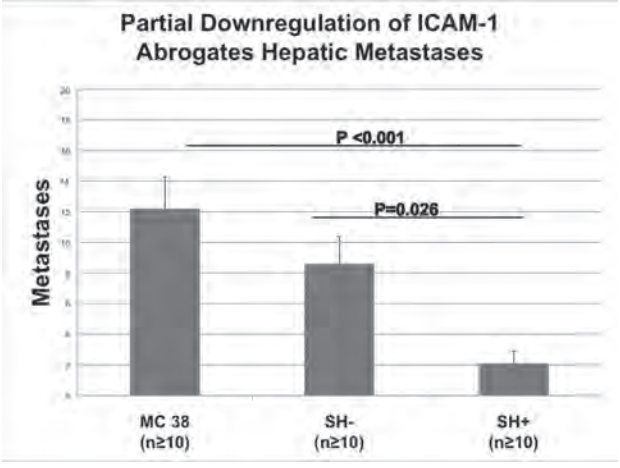
Downregulation of Intercellular Adhesion Molecule-1 (ICAM-1) Abrogates Hepatic Metastases in Murine Colon Adenocarcinoma K.K. Lo,* F. Gamboni, L. Ao, B. Edil, R. Schulick, C.C. Barnett. *University of Colorado, Aurora, CO.*

Background: ICAM-1 modulates cell-to-cell adhesion and is upregulated in malignant transformation of adenomas. Further, ICAM-1 upregulation has been demonstrated at the advancing margin of melanomas and pancreatic cancer. Collectively, these data suggest that upregulation of ICAM-1 promotes tumor progression. We hypothesize that downregulation of ICAM-1 will abrogate colon cancer hepatic metastases. Methods: To test this hypothesis, murine colon adenocarcinoma cells (MC38) were transduced with short-hairpin RNA (shRNA) lentivirus to downregulate ICAM-1 expression (SH+); MC38 cells were transduced with an empty vector-shRNA lentivirus to serve as vehicle control (SH-). C57/Bl6 mice were inoculated with tumor by splenic injection of 5 x10^4 cells and had subsequent hemi-splenectomy to prevent local tumor growth. 3 groups of mice received untransduced MC38 (n≥10), SH- (n≥10), or SH+ (n≥10) cells. Mice were sacrificed at 2 weeks and hepatic metastases counted by blinded observers. Statistical analysis was performed by ANOVA with Fischer's PLSD using p<0.05 to determine significance. Results expressed as mean±SEM. Results: Western blot and densitometry was performed probing for ICAM-1, which was constitutively expressed on MC38 cells. Transduction with shRNA downregulated ICAM-1 expression by 30% compared to MC38 cells. The mean ICAM-1 normalized optical density in SH+ (n=3) was .294 ±.019 compared to the MC38 (n=3) mean of .431 ± .033 (p<0.03). *In vivo*, mice receiving SH+ cells had significantly less metastases than mice receiving untransduced MC38 cells: 2.1±0.8 compared to 12.2±2.1 (p<0.001) respectively. SH+ mice also had significantly less disease than mice that received SH- cells: 2.1±0.8 compared to 8.6±1.8 (p=0.003) respectively. There was no difference in hepatic metastases in mice that received either SH- or MC 38 cells (p=0.1). Conclusion: Partial downregulation of ICAM-1 expression significantly decreases macroscopic colorectal cancer hepatic metastases in an

immunocompetent murine model. These data suggest that targeted downregulation of tumor expressed ICAM-1 may be a therapeutic option to limit colorectal cancer progression.



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Complement Inhibition: A Novel Form of Immunotherapy for Colon Cancer D. Magge,* Z. Guo, M. O'Malley, L. Francis, R. Ravindranathan, D.L. Bartlett. *University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: The complement system plays a role in the infiltration of myeloid derived suppressor cells into the tumor microenvironment. We hypothesize that complement inhibition will impede tumor growth due to enhanced CD8 cell activity in a colon cancer model. Methods: We tested the effect of C5 inhibition on tumor formation by injecting 10 C5 knock-out (C5KO) mice and 10 control C57Bl10 mice with 2x105 MC38 (colon cancer) cells subcutaneously (SQ). The mice were followed for tumor initiation and growth. This was repeated at 1X10*6 cells. We then tested the effect of cobra venom factor (CVF – a complement inhibitor) on tumor growth and immune cell infiltrates. 30 C57Bl6 mice were obtained, and our SQ colon cancer model was again established using an injection of 2x105 MC38 cells/mouse. Fifteen mice were treated with intraperitoneal (IP) 1mg/kg purified cobra venom factor (CVF) beginning on post-tumor implantation day (PTD) 2, receiving this agent every other day (qod). The remaining 15 mice were given 100µl PBS qod IP beginning on PTD 2. Tumor dimensions were measured, and tumors were harvested at 3 time points (5 mice/group). FACS analysis was performed on the tumor tissue, staining for CD4/CD8 cells. Results: With 105 MC38 cells injected, Only 2 (20%) C5KO mice had established subcutaneous tumors, while 100% of control mice established tumors. Tumor growth was significantly delayed in the 2 C5KO mice. A higher number of cells were injected in the 2nd experiment, but only 2 (20%) C5KO mice developed tumors, while 100% of control mice established our model. In our 3rd experiment, on PTDs 8 and 13, tumors in the CVF-treated mice were significantly smaller than those in the PBS-treated mice (p=.009; .004, respectively; Figure 1). On days 8 and 13, the %CD8 cells was significantly higher (p=.033; .045) and %CD4 cells was significantly lower (p=.04; .048) in the CVF-treated mice compared to the PBS-treated group. Conclusion: Complement inhibition retards the rate of tumor growth and alters the tumor microenvironment by encouraging infiltration of CD8 T cells. Complement inhibition may be an effective immunotherapy, either alone or in combination with other immune treatments.

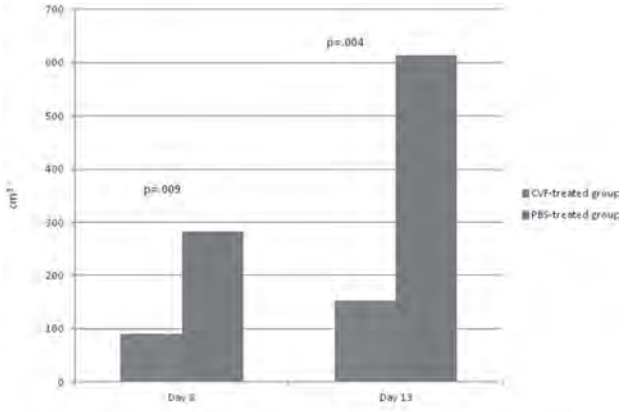

Figure 1 Tumor volume in CVF vs. PBS treated mice on Day 8 and Day 13.

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Phase II Trial of Neoadjuvant Oxaliplatin and Capecitabine (XELOX) and Bevacizumab Without Radiotherapy for Poor-risk Rectal Cancer K. Uehara,[1]* K. Hiramatsu,[2] A. Maeda,[3] E. Sakamoto,[4] M. Inoue,[5] S. Kobayashi,[6] Y. Tojima,[7] Y. Yoshioka,[1] G. Nakayama,[8] N. Ohmiya,[9] Y. Kodera,[8] H. Goto,[9] M. Nagino.[1] *1. Division of Surgical Oncology, Depertment of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan; 2. Department of Surgery, Toyohashi Municipal Hospital, Toyohashi, Japan; 3. Department of Surgery, Ogaki Municipal Hospital, Ogagi, Japan; 4. Department of Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Japan; 5. Department of Surgery, Handa City Hospital, Handa, Japan; 6. Department of Surgery, Toyota Kosei Hospital, Toyota, Japan; 7. Department of Surgery, Chukyo Hospital, Nagoya, Japan; 8. Department of Surgery II, Nagoya University Graduate School of Medicine, Nagoya, Japan; 9. Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Backgrounds: Preoperative chemoradiotherapy for locally advanced rectal cancer (LARC) reduces local failure, but it does not improve survival. The suppression of distant metastases is also important. Preoperative aggressive chemotherapy (CTx) may be a promising option for LARC. Methods: A multicenter phase II trial was undertaken to evaluate safety and efficacy of neoadjuvant XELOX and bevacizumab (Bv) in patients (pts) with LARC. Eligible pts had poor-risk rectal cancer and candidate for R0 resection. Poor-risk rectal cancer was defined by MRI findings; tumor extending to within 1 mm of or beyond the mesorectal fascia, tumor extending 5 mm or more into peripheral fat, cT4, or cN2. Pts received 4 cycles of capecitabine 2000 mg/m2 (d1-14), oxaliplatin 130 mg/m2 (d1) and Bv 7.5 mg/kg (d1) every 3 weeks. The last cycle did not include Bv. Surgical resection must be performed 3-8 weeks after the completion of CTx. Primary endpoint was the completion rate of scheduled treatments (CTx + surgery). Results: Between 2/2010 and 12/2011, 32 pts were enrolled (28M/4F). The depth of tumor was cT3 in 41%, cT4a in 28%, and cT4b in 31%. 38% of the pts had cN2. The median size of the tumor was 55.2 mm and the tumor was located at 45.5 mm from the anal verge. During CTx, grade 3/4 toxicity was experienced in 8 of 32 pts (25%). The completion rate of the scheduled CTx was 91%. The reasons for withdrawal were the pts refusal in 2 and disease progression in 1. Two of the 3 pts refused surgical resection and another underwent. Among 29 pts who completed scheduled CTx, one refused surgery within a given period and another had rectal penetration before planned surgery, requiring urgent laparotomy. As a result, the completion rate of this experimental treatment was 84%. R0 resection rate was 90% and the CRM+ rate was 17%. pCR rate was 13% and good tumor regression was exhibited in 37%. Any postoperative complications occurred in 43%. Conclusion: The completion rate and pCR rate were satisfying in poor-risk pts. Neoadjuvant XELOX and Bev might be a viable treatment option even for poor-risk LARC. (UMIN number, 000003507)

Table . Safty and efficacy

Completion rate of the scheduled CTx	29/32 (91%)
Surgical resection	30/32 (94%)
Treatment compliance (CTx + Surgery)	27/32 (84%)
Operation (AR/APR/TPE)	20/6/4
Postoperative complication	13/30 (43%)
R0 resection	27/30 (90%)
CRM (+)	5/30 (17%)
pCR (ypT0N0)	4/30 (13%)
Downstaging	23/30 (77%)

CTx: chemotherapy, AR: anterior resection, APR: abdominoperineal resection, TPE: total pelvic exenteration, CRM: circumferential resection margin, pCR: pathological complete response

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Perioperative Systemic Chemotherapy for Metastatic Appendiceal Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy A. Blackham,[1]* K. Swett,[1] C. Eng,[2] J. Sirintrapun,[1] S. Bergman,[1] K. Geisinger,[1] K.I. Votanopoulos,[1] J.H. Stewart,[1] P. Shen,[1] E. Levine.[1] *1. Wake Forest School of Medicine, Winston-Salem, NC; 2. University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: The role of perioperative systemic chemotherapy (pSC) in conjunction with cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS/HIPEC) for treating appendiceal cancer is unknown. Methods: A retrospective review of patients from two high volume centers (1999-2010) who received pSC within 3 months of CS/HIPEC for appendiceal peritoneal surface disease (PSD). A match-controlled analysis of patients with low grade histology was performed. All patients with high grade tumors were analyzed based on the use of pSC. Results: 22 patients with low grade PSD who underwent CS/HIPEC and received pSC were matched by resection status, age and lymph node status to patients who did not receive pSC. Median progression-free survival (PFS) was 29.5 months for patients treated with pSC compared to 37.0 months without pSC (p=0.18). There was a non-significant trend toward improved median overall survival (OS) with pSC (107 vs 72 months, p=0.46). CS/HIPEC was performed on 109 patients with high grade PDS: 70 were treated with pSC, while 39 were not. In comparing these two groups, there were no differences in lymph node status (p=1.0), resection status (p=0.84), age (p=0.71) or prior debulking surgery (p=0.68). The median OS (22.1 vs 19.6 months, p=0.74) and median PFS (10.9 vs 7.0 months, p=0.47) were similar in patients who received pSC compared to those treated without pSC. Progression while on preoperative SC was seen in 17% of patients, while 8% had a partial response and 73% had stable disease. Recurrence or progression while on adjuvant SC was seen in 25% of patients. The use of adjuvant SC resulted in longer PFS (13.6 months) compared to preoperative SC (6.8 months, p<0.01) and no pSC (7.0 months, p=0.03); however, it only trended toward better OS compared to preoperative SC (36.4 vs 16.0 months, p=0.06) and to no pSC (36.4 vs 19.6 months, p=0.14). Conclusions: These results suggest that there is a limited role for perioperative SC in low grade appendiceal PSD treated with CS/HIPEC. In contrast, patients with high grade appendiceal PSD demonstrate longer PFS following adjuvant SC.

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Learning Curve and Surgical Performance of Cytoreductive Surgery and Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei: A PSOGI Multicentric Study S. Kusamura,[1]* M. Deraco,[1] D. Baratti,[1] B. Moran,[3] P.H. Sugarbaker,[4] E. Levine,[5] E. Dominique,[6] D. Morris,[2] T. Chua,[2] A. Sardi,[7] O. Glehen,[8] F. Gilly,[8] P. Barrios,[9] A.G. Portilla,[10] I.H. J.T. de Hingh,[15] W.P. Ceelen,[13] J.W. Pelz,[14] P. Pompiliu,[16] S. Gonzalez-Moreno,[11] K. Van der Speeten,[12] T. Yan,[2] W. Liauw,[2] D. Goere,[6] C. Honore.[6] *1. Colorectal surgery department, Fondazione IRCCS Istituto Nazionale Tumori di Milano, Milano, MI, Italy; 2. Hepatobiliary and Surgical Oncology Unit, University of New South Wales Department of Surgery, St George Hospital, Sydney, NSW, Australia; 3. Basingstoke and North Hampshire NHS Foundation Trust, Basingstoke, United Kingdom; 4. Washington Cancer Institute, Washington Hospital Center, 106 Irving Street, NW, Suite 3900, Washington, WA; 5. Surgical Oncology Service, Wake Forest University Baptist Medical Center, Winston-Salem, NC, Winston-Salem, NC; 6. Department of Surgical Oncology, Institut Gustave Roussy, Cancer Center, Villejuif, France; 7. Division of Surgery, Department of Surgical Oncology, The Institute for Cancer Care, Mercy Medical Center, Baltimore, MD; 8. Department of Digestive Surgery, Centre Hospitalo-Universitaire Lyon Sud, Hospices Civils de Lyon, Pierre Bénite Cedex, Lyon, France; 9. Department of Oncological Surgery, Hospital Sant Joan Despí, Moises Broggi, Peritoneal Surface Malignancy Catalonian's Programme, Sant Joan Despí, Barcelona, Spain; 10. Department of General Surgery and Digestive Diseases, Hospital Santiago Apostol, Vitoria, Spain; 11. Peritoneal Surface Oncology Program, Department of Surgical Oncology, Centro Oncológico MD Anderson Cancer Center Madrid,, Madrid, Spain; 12. Department of Surgical Oncology, Ziekenhuis Oost-Limburg,, Genk,, Belgium; 13. Department of Gastrointestinal Surgery, University Hospital, De Pintelaan 185,, Ghent, Belgium; 14. Department of General-, Visceral-, and Paediatric Surgery, University of Wuerzburg,, Wuerzburg, Germany; 15. Department of Surgery, Catharina Hospital,, Eindhoven, Netherlands; 16. University Medical Center Regensburg, Regensburg, Germany.*

Introduction: the acquisition of proficiency in cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPCT) requires a long lasting learning process due to its complexity. Risk adjusted sequential probability ratio test (RA-SPRT) represents a useful method to monitor surgical performance. We compared, using RA-SPRT, the learning curves (LC) and surgical performances of international centers/surgeons in executing CRS+/-IPCT to treat pseudomyxoma peritonei (PMP). Methods: 2451 PMP cases were treated with CRS+/-IPCT (HIPEC/EPIC/both) by 39 operators from 33 international centers between February 1993 and February 2012. Both institution and surgeon based performances were evaluated, when the requirement of at least 50 procedures-experience for the former and 40 procedures for the latter was met. The target outcome was early oncological failure (EOF) defined as recurrence or death within 2 years from the surgery. RA-SPRT charts were plotted to assess whether the odds ratios (ORs) for EOF were <2.0 and setting $\alpha = \beta = 0.10$. Multivariate logistic regression model was elaborated using parameters related to institution (center-volume, annual case-load, etc), to tumor (PCI, histological subtype, etc), surgery (completeness of cytoreduction, type of IPCT, etc), and surgeon (background, training in CRS, etc) gathering a total of 15 independent factors. The breaking point (BP) for LC was defined as the moment in which the accept line was crossed by the RA-SPRT curve. Results: Rate of EOF was 29.0%. From the nine main centers, the BP for the LC was surpassed in 8, after a median of 99 procedures (range: 55-222). Two centers showed unacceptable performance at early phase of development. From the 12 main operators, the LC was overcome in 7, after a median of 73 procedures (range: 51-222). Conclusions: RA-SPRT confirmed that the LC of CRS+/-IPCT for PMP is extremely long warranting large scale referral mechanisms. In the actual international scenario of increasing popularity of CRS and HIPEC the availability of methods of quality control such as RA-SPRT is critical to favor the development of future accreditation systems.

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Gene Expression Profiles of Rectal Cancers with Mutant or Wild Type KRAS J. Garcia-Aguilar,[1]* Z. Chen,[2] C. Warden,[2] K. Avila,[1] N. Zhou,[2] Y. Yuan,[2] C. Chen,[1] M.R. Weiser.[1] *1. Memorial Sloan Kettering Cancer Center, New York, NY; 2. City of Hope, Duarte, CA.*

Introduction: The Kras oncogene is one of the most common mutations in colorectal cancer. Kras mutations are associated with increased tumor aggressiveness, poor response to selected targeted therapies, and reduced patient survival. We have previously shown that rectal cancers carrying a Kras mutation were less likely to achieve a pathologic complete response to radiation compared to tumors with wild type Kras. Our objective was to compare the gene expression profiles of rectal cancers with mutant and wild type Kras to identify genes that could be related to the Kras –dependent aggressive phenotype. Methods: Pretreatment biopsy tissue was collected from 120 patients with stages I, II and III rectal cancer treated in two prospective trials (NCT00335816 and NCT00114231). DNA and total RNA were extracted from microdissected cancer cells. Mutations in codons 12, 13, and 61 of the Kras gene were detected by pCR. 50ng of total RNAs were amplified to generate cDNA libraries using Ovation FFPE WTA System (NuGEN™ Technologies, Inc., San Carlos, CA). The amplified cDNA was labeled using the Encore Biotin Module, and hybridized to GeneChip® Human Genome U133A plus 2.0 arrays (Affymetrix, Inc., Cleveland, OH). Differences in gene expression between mutant and wild type Kras tumors were determined using T-test and Q-bound to correct for multiple testing by performing false discovery rate (FDR) analysis. Results: A total of 44 of 117 (37.6%) were mutant Kras. A total of 379 probes were upregulated and 262 were downregulated in tumors with Kras mutant compared to Kras wild type. Heatmap based on differentially expressed genes showed separation according to Kras mutant status. REG4 expression was increased 3 fold and CXCL5 was reduced 2.4 fold in tumors with mutant Kras compared to wild type Kras. The changes in expression on these genes are concordant with their known involvement in prognosis and response to therapy of colorectal cancer. Conclusions: The search for changes in gene expression in response to Kras activation led to identifying a number of genes associated with the tumor aggressive phenotype.

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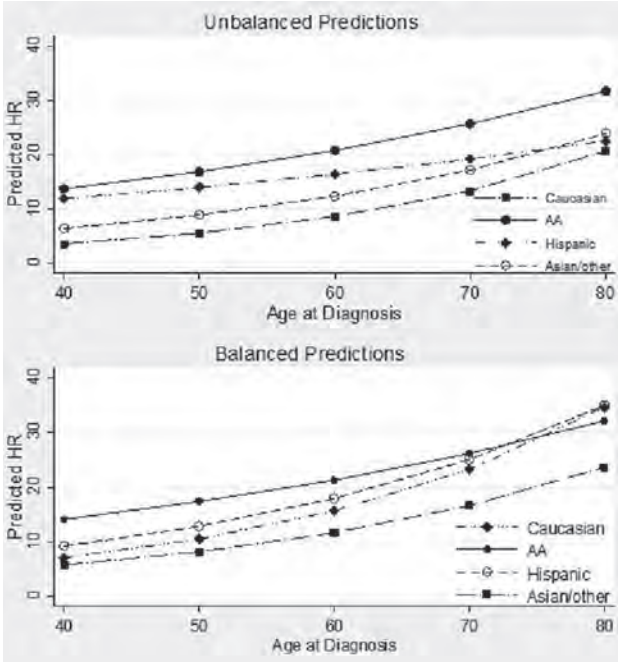
Understanding Race-Related Colorectal Cancer Survival Disparities U. Phatak,* L.S. Kao, T.C. Ko, C.J. Wray. *University of Texas Health Science Center at Houston, Houston, TX.*

Introduction Racial disparities in colorectal cancer (CRC) mortality have been well documented, and access to care and stage-specific treatment are thought to be contributing factors. We hypothesized that race-related CRC survival disparities may be partially explained by stage at diagnosis and treatment. Methods This study was conducted using 2 prospectively collected institutional tumor registries: 1from a public health system (2 hospitals), and 1 from a Not-for-Profit health system (9 hospitals) from 1995 to 2011. Patient demographics, stage at diagnosis, treatment, and survival were recorded. Hazard ratios (HR) were determined using Cox proportional hazards model and clustered for hospital. Standard regression diagnostics, including testing for interactions, and post-estimation analyses were conducted. Results Out of 6990 patients, 55.7% were Caucasian, 23.6% were African American (AA), 15.1% were Hispanic, and 5.6% were Asian/Other. More than half were male (n=3640, 52%). Variables predictive of survival in the Cox regression were surgery (HR 0.57, 95% CI 0.46-0.70), chemotherapy (HR 0.7, 95% CI 0.62-0.79), female gender (HR 0.87, 95% CI 0.83-0.90), age (HR 1.04, 95% CI 1.03-1.05) and AA race (with Caucasian as the reference) (HR 3.6, 95% CI 1.5-8.4). Since there was a statistical interaction between age and race, we conducted a post-estimation analysis with age fixed at 10 year intervals (see figure). Balancing stage, gender and treatment between racial groups reduced the predicted HRs by 28% for AAs and 17% for Hispanics across all decades. In the balanced model, AAs and Hispanics still had the worst predicted HRs at younger ages while Caucasians had the worst predicted HR after age 75. Conclusion Gender, stage and treatment partially accounted for worsened survival in African-Americans and Hispanics at all ages. At younger ages, race-related disparities remained which may reflect tumor biology or other unknown factors. Once gender, stage and treatment are balanced at older ages, the increased mortality seen in Caucasians may be due to other factors such as co-morbidities. Further system- and patient-level study is needed to investigate reasons for survival disparities.



Predicted hazard ratios by age and race with and without adjustment for stage, gender and treatment specific variables

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Only Intact Circulating Tumor Cells Predict Survival in Colorectal Cancer U. Bork,[1]* N. Rahbari,[2] B. Kasenda,[3] C. Reissfelder,[1] S. Schoelch,[2] M. Pfeifer,[2] W. Seibold,[2] J. Weitz,[1] M. Koch.[1] *1. Department of GI, Thoracic and Vascular Surgery, University Hospital Dresden, Dresden, Germany; 2. Department of Surgery, University Hospital Heidelberg, Heidelberg, Germany; 3. Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland.*

Introduction: Presence of circulating tumor cells (CTC) in patients with colorectal cancer (CRC) correlates with survival. CTC can be measured as cells positive for epithelial cell adhesion molecule (EPCAM) and cytokeratin (CK). Some cellular structures found in the blood may be positive for EPCAM and CK, and could be counted as CTC, although they do not fulfill criteria of intact cells. A recent study has shown a correlation between these objects and poor survival outcome in castration resistant prostate cancer patients. Here, we tested whether this tumor cell debris found in blood is a predictor of survival in CRC patients. Methods: 154 patients were included who underwent resection for CRC at our institution. We isolated EPCAM positive objects from patients blood and stained for DNA, CK and CD45. All EPCAM positive objects were subdivided into a predefined set of 6 morphological parameters. Results: The main objective of our study was to determine the prognostic impact of cellular objects positive for EPCAM and CK, but regarded as non-intact CTC. Endpoints were event free survival (EFS) and overall survival (OS). 19 of 154 patients (12%) were positive for granular CTC, which are not intact CTC. The association between granular CTC and UICC stage was not significant (p=0.574). All patients were positive for large tumor cell fragments (TCF). The median number of detected large TCF was 15 (range, 2-245). The median of detected small TCF was 1 (range, 0-55). . None of the six subgroups including various non-intact CTC objects showed an impact on EFS and OS in statistical analyses. There were no associations between distribution of any of these objects and UICC stage, either. However, EFS and OS were significantly correlated with intact CTC in all UICC stages. 19% of the patients were positive for intact CTC. Conclusions: EFS and OS correlated significantly with intact CTC in all UICC stages. In contrast to results in patients with castration resistant prostate cancer, no association was found for patients with CRC between non-intact tumor cell objects positive for EPCAM and CK on survival.

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The Use of Modified 4-Dimensional Computed Tomography in 100 Consecutive Patients with Primary Hyperparathyroidism: An Argument for the Abandonment of Sestamibi SPECT T.A. Platz,* A. Abdelhalim, A. Groman, W. Cance. *Surgical Oncology, Roswell Park Cancer Institute, Orchard Park, NY.*

Background: Four dimensional computed tomography (4D-CT) has emerged as an extremely sensitive preoperative imaging modality for primary hyperparathyroidism when compared to the historical use of sestamibi SPECT and ultrasound (US). Specialized volume rendering further enhances this technique which appears to be more beneficial for operative guidance than its counterparts. Methods: A total of 100 consecutive patients with non-recurrent primary hyperparathyroidism were evaluated from December 2010 to July 2012. All patients underwent modified 4D-CT with volume rendering which consisted of 3-dimensional reconstruction of the parathyroid pathology superimposed on relevant anatomic structures. Comparison was made to sestamibi SPECT and US for preoperative localization and intraoperative correlation. Radiation and billing analysis was completed. Results: All 100 patients underwent 4D-CT, 98 sestamibi SPECT and 91 US. 4D-CT was positive in 93 (93%) of 100 patients and correlated with operative findings in 87 (87%) compared to sestamibi SPECT which was positive in 54 (55%) of 98 patients and correlated with operative findings in 50 (51%). US was positive in 39 (43%) of 91 patients and correlated with operative findings in 37 (41%) of 91 patients. The false negative rate among 4D-CT, sestamibi SPECT and US were 7%, 45% and 57% respectively. Of the 44 patients with a false negative sestamibi SPECT, 35 (80%) of 44 had correlative 4D-CT's. Of the patients that had a negative 4D-CT, 1 had a positive US and 2 had a positive sestamibi SPECT which correlated to pathology (3%). Radiation exposure from 4D-CT was on average 49-58% less compared to that of sestamibi SPECT. Conclusion: Modified 4D-CT with volume rendering has multiple advantages compared to sestamibi SPECT including a significant higher operative correlation, lower false negative rate, and safer radiation profile. Consideration should be made for abandonment of sestamibi SPECT and US with use of 4D-CT as the preoperative imaging modality of choice.

Comparison of Preoperative Imaging Modalities

	True Postive (TP)	False Positive (FP)	False Negative (FN)
4D-CT	87%	6%	7%
Sestamibi SPECT	51%	7%	45%
Ultrasound	41%	5%	57%

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Minimally Invasive Parathyroidectomy is the Best Initial Operation for Patients with Localized Parathyroid Disease H. Wachtel,* M.C. Wismer, E.K. Bartlett, P.K. Shah, R.R. Kelz, G.C. Karakousis, D.L. Fraker. *Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA.*

Introduction: Greater than 80% of cases of primary hyperparathyroidism (pHPT) are caused by a single parathyroid adenoma. Patients with localized adenomas are candidates for minimally invasive parathyroidectomy (MIP). Intraoperative parathyroid hormone (IOPTH) monitoring allows the surgeon to confirm cure in the operating room. We studied our large single-surgeon series of parathyroidectomies performed for pHPT to compare cure rates between patients who underwent MIP versus bilateral neck dissection (BLNE). Methods: Between 2002-2011, 1160 consecutive patients underwent parathyroidectomy for pHPT. Operative technique was either MIP (n=516) or BLNE (n=644). MIP was defined as focused, unilateral neck exploration performed through a 2-3 cm incision. Variables examined included preoperative serum calcium level, 24-hour urinary calcium, parathyroid hormone (PTH) level, constitutional symptoms, nephrolithiasis, and osteoporosis. Primary outcome was cure, defined as ≥50% decrease of IOPTH into the normal range. Student's T test or Fisher's exact test were used as appropriate; a p-value of <0.05 was considered significant. Results: Patients undergoing MIP had a statistically but not clinically significant higher serum calcium (10.93 versus 10.74 mg/dl, p=2x10-5) than those who had BLNE. Otherwise there were no statistically significant differences between the MIP and BLNE cohorts. Of the 644 patients who underwent BLNE, 244 patients had localized disease. In this group, 41 (17%) had simultaneous thyroid surgery, 30 (12%) had ectopic or supernumerary glands, 12 (5%) had multiglandular disease, and 161 (66%) had adenomas which were discordant with preoperative imaging. Patients who underwent MIP had a higher cure rate than patients undergoing BLNE (100% versus 95.4%, p=3x10-7). 515 of 1160 patients (44%) were successfully cured with MIP. Conclusion: In our series, 44% of patients underwent successful MIP, with 100% cure rate. For patients with localized parathyroid adenomas, MIP augmented by IOPTH is highly effective and minimizes surgical morbidity. We conclude that for select patients MIP is the best initial operation.

Table I: Pre- and post-operative findings in pHPT patients undergoing minimally invasive parathyroidectomy (MIP) versus bilateral neck exploration (BLNE)

	Total Population (1160)	MIP (516)	BLNE (644)	P-value (MIP vs BLNE)
Gender				
Female (%)	898 (77)	392 (76)	506 (79)	0.32
Male (%)	262 (23)	124 (24)	138 (21)	0.32
Age (years)				
Mean (SD)	58.30 (13.01)	57.75 (12.55)	58.73 (13.42)	0.20
Pre-op serum Ca (mg/dl)				
Mean (SD)	10.83 (0.67)	10.93 (0.70)	10.74 (0.63)	$2x10^{-5}$
Pre-op 24H urinary Ca (mg)				
Mean (SD)	319.43 (168.39)	328.38 (161.51)	312.38 (173.60)	0.31
Pre-op PTH (pg/ml)				
Mean (SD)	110.70 (187.16)	111.43 (214.46)	110.11 (162.11)	0.92
Pre-op signs & symptoms				
Systemic symptoms (%)	763 (66)	354 (69)	409 (64)	0.07
Nephrolithiasis (%)	256 (22)	117 (23)	139 (22)	0.67
Osteoporosis (%)	640 (55)	285 (55)	355 (55)	1.00
Biochemical cure (%)	1130 (97.41)	516 (100.00)	614 (95.37)	$3x10^{-7}$

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Presentation, Management and Outcomes of Hyperparathyroidism in Octogenarians and Nonagenarians S.C. Oltmann, D. Schneider,* R.S. Sippel, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

Purpose Various elective surgical procedures are routinely performed on patients(pts) ≥80 years of age. With primary hyperparathyroidism (PHPT), surgical management is the only treatment. The goal of this study was to compare presentation and outcome of pts ≥80 to that of those <80 years of age. Methods Retrospective review of a prospectively collected database of all parathyroidectomies for PHPT performed at a university hospital. Pts ≥80 at the time of surgery were included in the study, and compared to pts <80 within the database. Data is expressed as means ± standard deviation. Results Between 2000 and 2012, 1839 pts underwent parathyroidectomy for PHPT. 155 pts were ≥80 at the time of surgery (8.4%), with ages ranging 80-91. Mean age 83.3±2.7, vs <80 (58.4±12.6, n=1684). ≥80 had higher PTH levels (147±87 vs 123±99) and creatinine levels (1.17±0.3 vs 1.01±0.7), and lower T-scores (-2.76±0.9 vs -1.77±2.8, p<0.01). Vitamin D levels were slightly higher not significant (33.7±15 vs 30.7±14 p=0.053). Calcium levels were similar (10.96±0.7 vs 11.02±0.88 p=0.46). ≥80 had a greater history of hypertension (78.7% vs 51.7%), coronary artery disease (30% vs 11.8%), congestive heart failure (14.2% vs 3.1%), and stroke (11% vs. 2%)(all p<0.01). Psychiatric disease was less common (9.7% vs 17.5% p=0.01). ≥80 had the procedure under local anesthesia only more often(14.8% vs 8.4% p=0.012). Use of unilateral approach was equivalent (70% vs 66% p=0.33). Rates of adenoma (84% vs 77%), double adenoma (6% vs 9%) and hyperplasia (11% vs 13% p=NS) were comparable. ≥80 required admission more frequently (44.7% vs 25.2% p<0.01), with longer length of stay (0.51 days ± 0.8 vs 0.27 ± 0.27, p< 0.01). Stays >24 hours were equivalent (2% vs 0.6% p=0.09). Complication rates were equivalent (3.9% vs 2.7% p=0.44). Conclusion Disease presentation of PHPT in pts ≥80 is similar to <80. Despite increased co-morbidities, parathyroidectomy is a safe procedure in this pt population with a noted equivalent complication rate to younger pts. Operative management remains the only treatment. Pt age should not be a deterrent to offer curative surgical intervention.

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Utility of Intraoperative Parathyroid Hormone Assay Following Parathyroidectomy with Four Gland Visualization K. Ahmed,* A. Alhefdhi, D. Schneider, R.S. Sippel, H. Chen, H. Mazeh. *university of wisconsin, Madison, WI.*

Background: Surgery is the only curative treatment in patients with primary hyperparathyroidism (PHPT). Modern tools such as intra-operative parathyroid hormone (ioPTH) assay helped reduce operative time and the extent

of surgery. However, the utility of ioPTH when all four glands are visualized remains questionable. The aim of this study was to determine the added value of ioPTH assay following parathyroidectomy with four gland visualization in patients with PHPT. Methods: A retrospective review of patients that underwent parathyroidectomy for PHPT between July 2001 and February 2012 by two experienced endocrine surgeons was performed. Included were patients with operative reports indicating that all four parathyroid glands were identified. ioPTH was measured to confirm cure. Cure was defined as at least 50% fall by 15 minutes post excision as compared to pre-incision levels. The operative reports were reviewed to determine the effect of ioPTH on the surgical procedure. Results: Of 1,838 patients that underwent parathyroidectomy, four glands were visualized in 238 (13%). Single adenoma was identified in 28 (12%) patients, double adenoma in 52 (22%), and four gland hyperplasia in 157 (65%) patients. Of the patients included in this study, ioPTH fell to the cure criteria in 235 (98%) of the patients, and inadequate drop was documented in 3 (2%) patients. Of the three patients where ioPTH drop was inadequate, all were found to have multigland disease. Further exploration was performed in all three patients; however, in only one patient (0.4%) was a fifth parathyroid gland was identified and resected. In all three cases ioPTH did not affect the ultimate outcome or cure rate. Conclusions: In our experience, once four parathyroid glands were visualized, ioPTH affected the surgical procedure in only 1/238 (0.4%) patients. Nevertheless, ioPTH did not affect the surgical outcome in any of the patients and therefore has limited role following four glands visualization by very experienced surgeons.

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Predictors of Radioactive Iodine Ablation Use for Micropapillary Thyroid Carcinoma over Two Decades A.W. Chae,* S.R. Martinez, A.D. Yang. *University of California-Davis, Sacramento, CA.*

Background: Radioactive iodine (RAI) is not routinely recommended for the adjuvant treatment of micropapillary thyroid carcinoma (MPTC). We aimed to report on clinical and pathologic factors associated with use of RAI in this patient population. Methods: The Surveillance, Epidemiology, and End Results database was queried for patients who underwent surgery for MPTC (tumor size ≤ 1 cm) from 1988 to 2009. We excluded patients without a biopsy-proven diagnosis, those diagnosed at autopsy, and patients with documented extrathyroidal extension. Patients were further stratified by lymph node status. Multivariate logistic regression models predicted use of RAI based upon patient, tumor, and treatment-related factors. Results: Among 24,076 patients with MPTC, 23,748 (98.6%) had complete information on the use of RAI and were eligible for study inclusion. Of these, 6,172 (26%) received RAI. Lymph node status was known for 8,230 (34.7%). Node metastasis was present in 23.8%. On multivariate analysis of all patients, an increasing number of positive nodes (OR 1.24, CI 1.19-1.29; p<0.001), increasing tumor size (OR 1.17, CI 1.15-1.19; p<0.001), Asian race (OR 1.39, CI 1.15-1.66; p<0.001), and male sex (OR 1.20, CI 1.05-1.37; p=0.007) predicted use of RAI. RAI use was less likely with advancing age (OR 0.99, CI 0.99-1.00; p<0.001), in those with an increasing number of lymph nodes examined (OR 0.99, CI 0.99-1.00; p=0.049) and those undergoing thyroid lobectomy (OR 0.16, CI 0.13-0.20; p<0.001), nodulectomy (OR 0.12, CI 0.04-0.41; p=0.001), subtotal thyroidectomy (OR 0.45, CI 0.36-0.57; p<0.001), or thyroidectomy NOS (OR 0.51, CI 0.27-0.98; p=0.042). Among node-negative patients, Asian race and increasing tumor size predicted RAI. Factors predicting decreased use of RAI were an increasing number of lymph nodes examined, unknown race, less than total thyroidectomy, and advancing age. Conclusions: A significant number of MPTC patients receive potentially unnecessary RAI. Patients with MPTC and the physicians who treat them should be educated about the appropriate use of this important adjuvant treatment.

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Targeted Drug Delivery with Octreotide-Conjugated Unimolecular Micelles in Medullary Thyroid Cancer J.F. Burke,[1]* W. Xu,[2] S. Pilla,[2] A. Dammalapati,[1] H. Chen,[1] S.S. Gong,[2] R. Jaskula-Sztul.[1]
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Introduction: Medullary thyroid cancer (MTC) is a neuroendocrine tumor (NET) that is relatively insensitive to standard chemotherapies. Resveratrol suppresses MTC growth in vitro but has difficulty reaching therapeutic doses in vivo. Multifunctional polymer nanoparticles are a novel drug delivery platform that specifically target tumor cells. We developed an octreotide-conjugated unimolecular micelle loaded with resveratrol and evaluated the effects of treatment on MTC cells. Methods: Unimolecular micelles were formed by hyperbranched amphiphilic block copolymers. The core of the unimolecular micelle is Boltorn H40, a hyperbranched aliphatic polyester. The inner hydrophobic layer is polylactide (PLA) and the outer hydrophilic layer is poly(ethylene glycol) (PEG). The NET-targeting ligand, octreotide (OCT), was selectively conjugated onto the PEG segments. Components were combined to make 4 aliquots: targeted and loaded with resveratrol (Oct-Res), non-targeted and loaded (Res), targeted and not loaded (Oct), and non-targeted not loaded (Empty). Human MTC-TT cells were treated with aliquots and free resveratrol and cell growth was assessed with MTT assays. Production of NET marker achaete-scute complex-like 1 (ASCL1) was evaluated with Western blot analysis. Results: Unimolecular micelles had a uniform size distribution and controlled drug release behavior. All aliquots suppressed cell growth compared to controls ($p \leq 0.001$), but only the Oct-Res micelles suppressed growth to the same level as free resveratrol through 6 days of treatment. In MTC-TT cells treated for 4 days with 50 μM aliquots, ASCL1 was reduced by Oct-Res and Res micelles and free resveratrol, while ASCL1 levels were similar to controls in Oct and Empty micelle lysates. Conclusions: Resveratrol loaded in OCT-conjugated unimolecular micelles targeted to NETs affected MTC cells similarly to free resveratrol in vitro, with equal growth suppression and reduction in NET marker production. OCT-conjugated unimolecular micelles suppressed growth more effectively than non-targeted ones. These results suggest that OCT-conjugated unimolecular micelles will effectively translate to future in vivo studies.

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Small Bowel Carcinoid: Location Isn't Everything! D.M. Hari,[1]* A.M. Leung,[1] H.M. Reich,[2] M. Sim,[1] J. Lee,[1] E.M. Wolin,[2] F. Amersi.[2]
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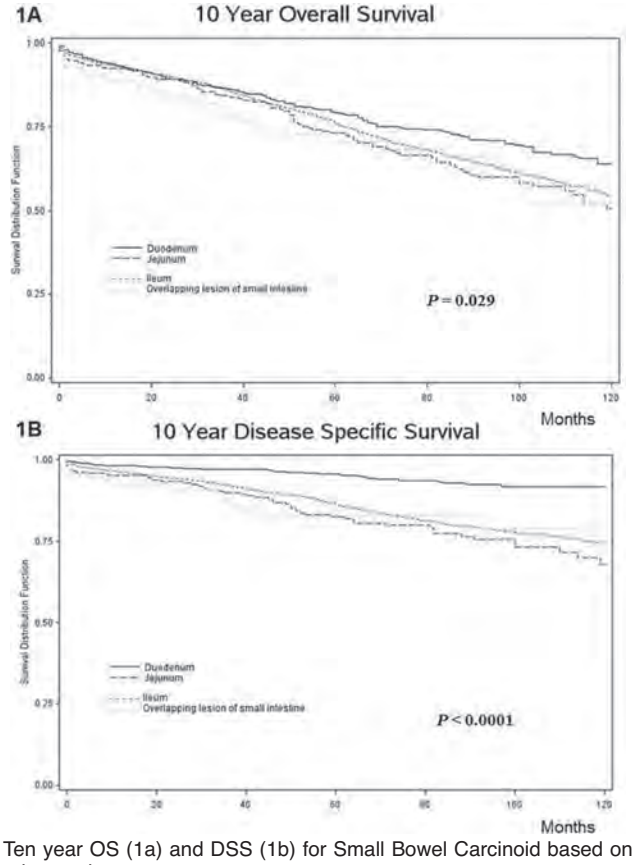
Introduction: Contemporary data has revealed that small bowel carcinoid (SBC) accounts for the majority of gastrointestinal carcinoids. However, data remains limited regarding prognostic factors that impact survival for SBC patients. Using a population-based analysis, we investigate the significance of the primary site of disease for SBC. Methods: The Surveillance, Epidemiology, and End Results database was queried for histologically confirmed SBC between the years 1988 and 2009. Patients were excluded if adequate demographic and staging information was unknown. Overall and disease survival curves (OS and DSS respectively) were analyzed using the Kaplan-Meier method and compared using Log rank testing. Log rank and multivariate Cox regression analysis was used to identify predictors of survival using age, year of diagnosis, race, gender, tumor histology/size/location, TNM stage, number of lymph nodes (LNs) examined and percent of LNs with metastases. Results: Of the 3834 patients analyzed, the mean age was 62.13 years and 51.2% were male. Median follow up was 50 months. The 10-year OS (Figure 1a) and DSS (Figure 1b) for duodenal primaries was statistically significant when compared to ileal, jejunal and overlapping primaries (P = .0290 and < .0001, respectively). However, more the 90% of duodenal primaries had Stage I and II disease only. On multivariate Cox regression analysis, after adjusting for multiple factors, primary site location was not a significant predictor of survival (P = .948 for OS and = .625 DSS) while TNM stage, age, tumor size and number of LNs examined portend improved OS and DSS. Conclusions: This population-based study of SBC over the past 30 years refutes the concept that the location of the SBC influences survival. A key element to consider is that more than 90% of duodenal primaries present at early stages. Further screening and diagnostic methods to detect other SBC primary sites could significantly impact survival.



Ten year OS (1a) and DSS (1b) for Small Bowel Carcinoid based on primary site

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Overexpression of Membrane Proteins in Primary and Metastatic Gastrointestinal Neuroendocrine Tumors J.C. Carr,* S.K. Sherman, D. Wang, M. O'Dorisio, T.M. O'Dorisio, J.R. Howe. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: The incidence of neuroendocrine tumors (NETs) has risen 5-fold over the past 30 years and many patients present with advanced disease. We recently identified receptors and membrane proteins with significant up or down-regulation in a limited sample of small bowel (SBNET) and pancreatic (PNET) NETs. This study set out to validate expression patterns of these genes in a larger group of primary NETs, and to determine whether these findings extend to liver and lymph node metastases. Methods: Primary tumors, normal tissue, and nodal, and liver metastases were collected at surgery in patients with SBNETs and PNETs. RNA was extracted and qPCR performed on 6 genes selected previously from whole genome and G-protein coupled receptor (GPCR) arrays. Results of triplicate experiments were normalized to housekeeping genes GAPDH and POLR2A. Significance was assessed by Student's t-test of normalized mean threshold cycles. Results: Expression fold-changes compared to normal tissue from 32 PNETs (plus 8 nodal and 5 liver metastases) and 42 SBNETs (plus 32 nodal, 24 liver metastases) are shown in the Table (* equals $p<0.01$). The secretin receptor (SCTR) and adenosine A1 receptor (ADORA1) were significantly underexpressed in PNETs and their metastases, while the oxytocin receptor (OXTR) was significantly overexpressed in primaries and metastases of both SBNETs and PNETs. Normal tissues showed minimal OXTR expression. PNET primaries significantly overexpressed MUC13 and MEP1B, but low numbers of nodal and liver metastases precluded finding significance in these tissues. SBNETs significantly overexpressed OXTR as well as GPR113 in primary tumors and metastases. Expression fold-changes seen in primary tumors were more pronounced in most nodal and liver metastases. Conclusions: OXTR is significantly overexpressed relative to normal tissue in primary PNETs, SBNETs and also in their liver and lymph node metastases. Low expression in normal tissue with elevated expression in primary and metastatic tumors make OXTR an intriguing target for new imaging and therapeutic interventions. GPR113 is overexpressed in SBNETs and may be a target in these tumors as well.

	Pancreas			Small Bowel		
	Primary	Liver	Node	Primary	Liver	Node
SCTR	-31.8*	-167.0*	-305.9*	-2.5*	-1.8	-6.4*
ADORA1	-9.7*	-35.3*	-25.0*	1.0	-2.1	-1.0
OXTR	18.2*	42.7*	49.4*	167.4*	184.2*	467.4*
GPR113	2.6	2.0	3.6	8.2*	15.2*	18.0*
MUC13	9.3*	4.0	7.4	1.5	1.1	-1.6
MEP1B	13.0*	174.3	9.9	-3.9	-70.7*	-103.2*

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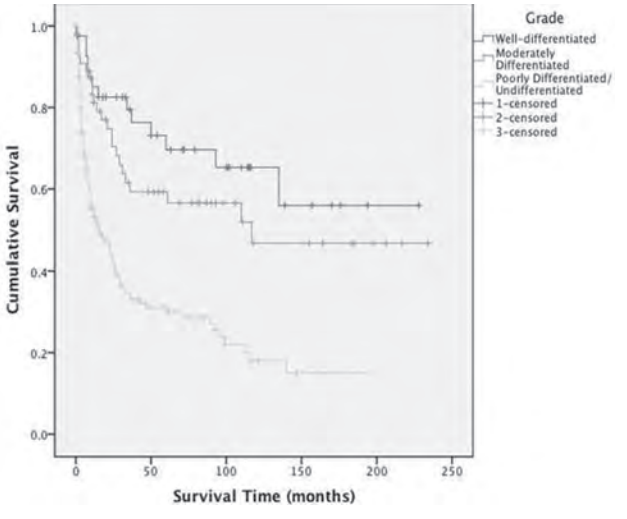
Surgical Management of Advanced Adrenocortical Carcinoma: AJCC Prognostic Factors T.B. Tran,* V.G. Menon, D. Liou, N.N. Nissen. *Cedars-Sinai Medical Center, Los Angeles, CA.*

Introduction: Adrenocortical carcinoma (ACC) is a rare tumor with poor prognosis, often diagnosed in the late stages of the disease because of the tumor's indolent behavior. The American Joint Committee on Cancer (AJCC) staging system is used to determine prognosis based on tumor size, lymph node status, and presence of metastases, but its ability to predict survival remains variable. We aim to critically review the current AJCC staging system and identify current management and prognostic factors for survival. Methods: A total of 1242 patients, diagnosed with ACC between 1988 and 2009 were identified from the Surveillance, Epidemiology End Results Registry (SEER). Kaplan-Meier curves and log-rank tests were used to identify differences in overall survival for ACC. Prognostic factors for survival were identified through multivariate analysis using Cox regression method. Results: Analysis of the AJCC staging system identified several factors, affecting prognosis. Of those patients who underwent lymphadenectomy (15.8%) and found to have positive lymph nodes, having more than 2 affected lymph nodes is associated with poor 5- and 10-year survival compared to those with 1 affected lymph node ($p<0.001$). Median tumor size was 11cm. Tumor size was also a significant predictor of survival ($p=0.004$). Associated with the pathology, but not a part of the AJCC staging system, multivariate analysis showed that tumor grade was the most significant prognostic factor affecting survival for all stages of ACC (graph). In addition, surgical resection provides increased survival in those with Stage III and Stage IV disease ($p=0.021$ and $p<0.001$ respectively) compared to radiation therapy alone. Conclusions: This analysis suggests that the inclusion of grade of tumor may result in an improved and more effective staging system. In addition, increased lymphadenectomy at the time of surgery may also improve staging and prognostication. Though surgery has been shown to improve long-term survival for ACC, a novel staging system that incorporates grade and number of positive lymph nodes may also greatly impact future management and outcomes of patients with advanced adrenocortical carcinoma.



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Adrenalectomy Provides Survival Benefit for Patients with Distant Adrenal Metastases G. Howell,* M.J. Armstrong, M.T. Stang, K.L. McCoy, D.L. Bartlett, S.E. Carty, L. Yip. *Surgery, University of Pittsburgh, Pittsburgh, PA.*

Introduction: The adrenal gland is a frequent site of distant metastases, but the therapeutic benefit of adrenal metastasectomy is controversial. The purpose of this investigation is to determine if adrenalectomy for curative intent improves survival and to elucidate factors that may bear prognostic significance. Methods: We conducted a single center, retrospective review to identify a consecutive series of patients with adrenal metastases who had adrenalectomy performed with curative intent between 2000-2012. Survival time was calculated from date of primary cancer diagnosis to last follow-up or death. Clinical variables were examined for association with survival. Results: Analysis included 63 patients, 56% (35/63) male, with mean age of 60 years (range 23-82), and mean follow-up of 57 months (range 7-243) from primary cancer diagnosis. The most common primary tumor was lung (31), followed by kidney (8), melanoma (4) and colon (4). Synchronous adrenal metastases were diagnosed in 8/63 (13%) patients. In the remaining 55 patients with metachronous adrenal metastasis, mean time to development was 32 months (range 4-217). At last follow-up 43% (27/63) of patients were disease free, 43% (27/63) had experienced recurrence, 3% (2/63) had persistence due to underestimated disease burden, 8% (5/63) had progression of their unresected primary, and 3% (2/63) died in the immediate perioperative period. Median overall survival was 44 months, with 55% survival at 5 years. Patients with a diagnosis of lung primary had poorer outcome with median overall survival of 31 months and 33% survival at 5 years (p=0.003). Univariable analysis further revealed worse survival for patients with synchronous metastases (p<0.001), and shorter time interval from primary diagnosis to adrenalectomy (p=0.034). No significant association was found for gender (p=0.45) or age (p=0.82). Conclusion: Adrenal metastasectomy can offer survival benefit and render patients free of disease when performed with curative intent. Resection should be considered even in patients with lung cancer metastasis whose survival in this large series exceeded published rates for stage-matched controls.

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Microwave Ablation for Hepatic Malignancies: A Multi-Institutional Analysis R.T. Groeschl,[1]* C.H. Pilgrim,[1] E.M. Hanna,[2] K.A. Simo,[2] R.Z. Swan,[2] D. Sindram,[2] J.B. Martinie,[2] D.A. Iannitti,[2] M. Bloomston,[3] C. Schmidt,[3] H. Khabiri,[3] L.A. Shirley,[3] R.C. Martin,[4] K.K. Christians,[1] W.S. Rilling,[1] T. Gamblin.[1] *1. Medical College of Wisconsin, Milwaukee, WI; 2. Carolinas Medical Center, Charlotte, NC; 3. Ohio State University, Columbus, OH; 4. University of Louisville, Louisville, KY.*

INTRODUCTION: Although many hepatobiliary centers have moved from radiofrequency ablation to microwave ablation (MWA), the factors that influence local control with MWA are not well described. We hypothesized that tumor size, number of tumors, and tumor histology significantly affected MWA success and recurrence-free survival (RFS). METHODS: Consecutive patients with hepatic malignancy treated by MWA were included from 4 high-volume institutions (2003-2011), and grouped by histology: hepatocellular carcinoma (HCC), colorectal metastases (CM), neuroendocrine metastases (NM), and other cancers. Fisher's exact and Kruskal-Wallis tests compared group characteristics. Independent significance of outcome variables was established with logistic regression and Cox proportional hazards models. RESULTS: Four-hundred seventy three ablation procedures were performed (139 HCC, 198 CM, 61 NM, and 75 other) for a total of 875 tumors. Patient and tumor characteristics are shown in Table 1. Median follow-up was 18 months. Concurrent hepatectomy was performed in 178 patients (38%). Thirty-day morbidity and mortality rates were 18.4% and 0.8%, respectively. Complete ablation was confirmed for 839 of 865 tumors (97.0%) on follow-up cross-sectional imaging. NM had greater odds of an incomplete ablation compared to other histologies (odds ratio: 3.07, 95% confidence interval [CI]: 1.08-8.67, p=0.035), however this was not significant in adjusted models. The local recurrence rate was 6.1% overall, and was highest for HCC tumors (10.3%, p=0.051). RFS did not vary significantly between histologies. In multivariable models, tumor size ≥3cm was the only variable predicting poorer RFS (hazard ratio: 1.60, 95% CI: 1.02-2.50, p=0.039). Independent predictors of poorer OS included age, number of tumors ablated, and tumor size ≥3cm. CONCLUSIONS: In this large dataset, patients with ≥3cm tumors showed a propensity for early recurrence, regardless of histology. Higher rates of local recurrence were noted in HCC patients, which may reflect underlying liver disease. Accounting for recurrence at any site, however, there were no significant differences in RFS between tumor histologies.

Characteristics and Outcomes of 473 Microwave Ablations for Liver Cancer, by Tumor Histology.

Variable	HCC n = 139	CM n = 198	NM n = 61	Other n = 75	Total n = 473	p
Median age, yrs (range)	62 (46-90)	60 (27-87)	57 (25-82)	60 (26-81)	60 (25-90)	0.005
Median # tumors ablated (range)	1 (1-4)	1 (1-14)	2 (1-11)	1 (1-6)	1 (1-14)	<0.001
Median largest tumor size, cm (range)	2.6 (0.7-6.0)	2.0 (0.5-6.5)	2.0 (0.9-11.0)	2.5 (0.9-6.0)	2.0 (0.5-11.0)	0.017
Gender, n (%)						<0.001
Female	29 (21)	76 (38)	31 (51)	44 (59)	180 (38)	
Male	110 (79)	122 (62)	30 (49)	31 (41)	293 (62)	
Route of Ablation, n (%)						<0.001
Open	22 (16)	135 (68)	50 (82)	35 (47)	242 (51)	
Laparoscopic	98 (70)	46 (23)	9 (15)	33 (44)	186 (39)	
Percutaneous	19 (14)	17 (9)	2 (3)	7 (9)	45 (10)	
Concomitant Hepatectomy, n (%)						<0.001
No	122 (88)	97 (49)	26 (43)	50 (67)	295 (62)	
Yes	17 (12)	101 (51)	35 (57)	25 (33)	178 (38)	
Complete Ablation, n (%) (n = 875 total tumors ablated)	n=169	n=403	n=202	n=101	n=875	0.166
No	7 (4)	7 (2)	9 (4)	3 (3)	26 (3)	
Yes	159 (94)	393 (97)	191 (95)	96 (95)	839 (96)	
Unknown	3 (2)	3 (1)	2 (1)	2 (2)	10 (1)	
Recurrence-Free Survival						0.283
Median, months	24.9	24.5	33.0	24.9	26.8	
3-year, %	34	34	36	31	34	
5-year, %	7	9	11	9	9	
Overall Survival						0.002
Median, months	27.1	32.1	91.9	25.5	33.9	
3-year, %	38	45	70	48	47	
5-year, %	19	17	54	23	22	

HCC = hepatocellular carcinoma
CM = colorectal metastases
NM = neuroendocrine metastases

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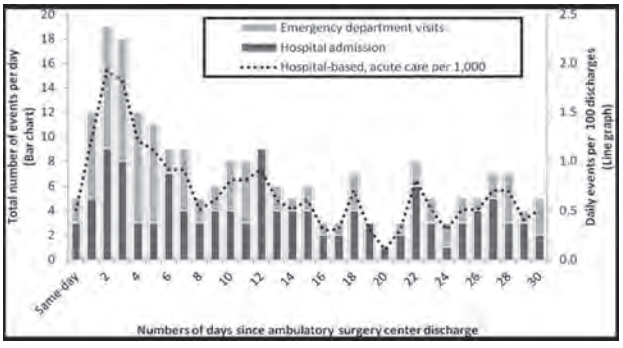
Hospital-based, Acute Care Encounters Following Radiofrequency Ablation of Hepatic Tumors R.M. Tuttle,* J. Fox, M. Hellan, J. Ouellette. *Wright State University, Dayton, OH.*

Introduction: Adverse events during index hospitalization for radiofrequency ablation (RFA)have been studied and deemed to be low. However, the need for hospital-based, acute care evaluation and treatment following discharge has not been well described. We conducted this study to describe hospital-based, acute care utilization following RFA for cancer within 30-days. Methods: Using data from the California state ambulatory surgery, inpatient, and emergency department databases, we identified all state residents >40 years of age who underwent RFA of primary or metastatic hepatic tumors without concurrent liver resection between January 2008 and September 2010. We then determined how frequently this population visited the emergency department or were readmitted to the hospital within 30-days as a rate per 100 discharges. Additionally, we constructed a multivariable regression model to determine which patient-level factors were significantly associated with hospital return. Results: We identified 1,094 patients treated at 87 hospitals. Most patients were >60 years of age (%), male (61.4%), and underwent radiofrequency ablation for primary malignancy (52.7%) by an open (21.9%), percutaneous (46.5%), or laparoscopic (25.5%) approach. The observed hospital readmission, emergency department visit, and overall hospital-based, acute care rate per 100 discharges was 11.1, 8.8, and 19.8 respectively. Most encounters occurred within the first 7-days of discharge for complications (infections or bleeding) or abdominal pain. In multivariable analysis, a history of complicated diabetes (adjusted OR=2.36, 95% confidence interval [1.06-5.28]), coagulopathy (2.00 [1.23-3.24]), fluid and electrolyte disorder (1.75 [1.18-2.59]), drug abuse (2.28 [1.00-5.23], and depression (2.24 [1.36-3.69]) were associated with hospital return within 30-days of discharge. Conclusions: Hospital-based acute care for post-procedure complications or symptoms after RFA is common. Specific patient-level factors are associated with these return encounters and may warrant preoperative identification, optimization or targeted intervention.



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Optimal Stroke Volume Variation in Hepatic Resection: A Replacement for Standard Central Venous Pressure Monitoring

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INTRODUCTION: Central venous pressure (CVP) is the standard method of volume status evaluation during hepatic resection. Considering the increased emphasis on reducing central line infections, there may be a benefit to eliminating central venous access needed to perform CVP monitoring. Stroke volume variation (SVV) is a new parameter that can be used to predict an individual's volume load through an existing arterial line. The aim of this study was to determine if SVV is as safe and effective as CVP in measuring volume status during hepatic resection. METHODS: Two cohorts of 40 consecutive patients (80 total) were evaluated during hepatic resection between 12/2010 and 8/2012. The initial evaluation group of 40 patients had continuous CVP monitoring and SVV monitoring performed simultaneously in order to establish appropriate SVV parameters for hepatic resection. A validation group of 40 patients was then monitored with SVV alone to confirm the accuracy of the established SVV parameters. Type of hepatic resection, transection time, blood loss, complications and additional operative and post-operative factors were collected prospectively. SVV was calculated using the FlotracTM System. RESULTS: The evaluation group had a median age of 62 (29-82), median BMI 27.7 (16.5-40.6), 18 laparoscopic, 22 open, and 24 undergoing major (≥3 segments) hepatectomy. Median transection times were 43 minutes (range 20 – 65), median blood loss 150cc (20-950), with no pringle maneuver utilized. In this evaluation group a CVP of -1 to 1 significantly correlated to a SVV of 18-21 ($R2 = 0.85$, $p<0.001$). The validation group had a median age of 61 (35-78), median BMI 28.1 (17-41.2), 24 laparoscopic, 16 open, and 33 undergoing major hepatectomy. Using a SVV goal of 18 to 21, median transection time was 55 minutes (25-78), median blood loss of 225cc (100-1150), again without the use of a pringle maneuver. CONCLUSIONS: SVV is as accurate a predictor of fluid status as CVP monitoring during hepatectomy. The ability to avoid invasive central venous access could potentially reduce central line related complications with equivalent safety during hepatic resection.

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Identification of a *Bona Fide* Biomarker of MicroRNA in Serum Exosomes to Predict Recurrence of Hepatocellular Carcinoma after Liver Transplantation

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Background: The predictive biomarker for the recurrence of hepatocellular carcinoma (HCC) has great benefit on the selection of treatment options including liver transplantation (LT) for HCC. Micro RNA (miR), a class of small non-coding RNA molecule, affect crucial processes in cancer development and offer great potential as biomarkers for cancer due to their remarkable stability in blood. The objective of this study is to identify specific miRs in exosomes of HCC recurrence from the serum and bone marrow of the patients and validate these molecules as novel biomarkers for HCC recurrence. Methods: We employed microarray-based profiling of miR expression from exosome in serum and bone marrow of the patient with HCC to define a biomarker that distinguishes between patients with and without HCC recurrence after liver transplantation or hepatic resection. This was followed by a real-time semi-quantitative PCR validation in a separate cohort of 63 HCC patients who underwent living related LT. Result: We found that 4 miRs which were differentialy (>2 folds) expressed in the serum exosome with HCC cases that had recurrence after LT compared to those without recurrence. They were associated with tumor aggressiveness of HCC in the validated cohort series. To disclose the original cell fraction of each identified miR in bone marrow, we divided bone marrow cells into 3 fractions by cell surface markers, such as CD14+ (macrophage), CD14-/CD45- (lymphocyte) and CD14-/CD45-/EpCAM+ (epithelial cell), then we performed microRNA microarray in each fraction. The increased expression of miR-150, miR-135a, and miR-1225-5p were observed in the CD14-/CD45+ fraction of bone marrow of HCC cases with recurrence, which suggested the association of CD4+ lymphocyte impairment and tumor recurrence. Conclusions: Circulating miR in serum exosome has potential as a novel biomarker to predict recurrence of HCC. MiR profiling of serum and bone marrow may help to clarify the mechanism of recurrence of HCC. The identified miR/gene axis indicated that the disruption of the immune systems after LT should provoke the recurrence of HCC in the future.

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A Multi-Institutional Analysis of Recurrence-Free and Overall Survival: Prognostic Factors in Patients with Hepatocellular Carcinoma in a Non-Cirrhotic Liver

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Background: Hepatocellular carcinoma (HCC) primarily affects patients with a cirrhotic liver. As such, reports on the characteristics of patients with HCC in the setting of a non-cirrhotic liver, as well as predictors of recurrence and survival, are scarce. Methods: Between 1992-2011, 334 patients treated for HCC in a non-cirrhotic liver were identified from 3 major hepatobiliary centers. Clinicopathological characteristics were analyzed and independent predictors of recurrence and overall survival were identified using Cox proportional hazards regression models. Results: Median patient age was 58 years and 23% were female. Most patients had a solitary tumor (81%); median tumor size was 6.5 cm and 56% of patients had a poorly or undifferentiated tumor. The majority of patients (96%) underwent liver resection, while a minority had ablation (4%). Among patients who underwent resection, surgical margins were negative in 303 (94%). Median, 1- and 5-year recurrence-free survival was 2.4 years, 66.9%, and 27.2%, respectively. Poor tumor differentiation [HR=1.76], macrovascular invasion [HR=2.43], and the presence of satellite lesions [HR=2.50] were independently associated with a shorter disease-free interval; in contrast, an intact tumor capsule was independently associated with longer recurrence-free survival [HR=0.47] (all $P<0.05$). Median, 1- and 5-year overall survival was 5.9 years, 85.7%, and 52.5%, respectively. Similar variables were independently associated with shorter overall survival including tumor size ≥ 5 cm [HR=2.07], poor tumor differentiation [HR=2.46], macrovascular invasion [HR=3.38], presence of satellite lesions [HR=2.56], and adjacent organ invasion [HR=13.22] (all $P<0.05$). Conclusion: Following resection of HCC in the setting of no cirrhosis, over one-half of patients were alive at 5-years. However, even among patients with no cirrhosis, recurrence was common. Factors associated with disease-free and overall survival included tumor characteristics such as tumor grade, vascular invasion, and presence of satellite lesions.

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Analysis of Toxicity and Outcomes in Patients Undergoing Hyperthermic Isolated Hepatic Perfusion with Melphalan for Metastatic Melanoma to the Liver B.J. Golas,[1]* D. Magge,[1] A.H. Zureikat,[1] H.J. Zeh,[1] H.R. Alexander,[3] S.K. Libutti,[5] R.E. Royal,[4] M.P. Holtzman,[1] M.S. Hughes,[2] K.K. Turaga,[6] S.G. Pappas,[6] T. Gamblin,[6] D.L. Bartlett,[1] J.F. Pingpank.[1] *1. University of Pittsburgh, Pittsburgh, PA; 2. Surgery Branch, National Cancer Institute, Bethesda, MD; 3. University of Maryland, Baltimore, MD; 4. MD Anderson Cancer Center, Houston, TX; 5. Albert Einstein/Montefiore Medical Center, New York, NY; 6. Medical College of Wisconsin, Milwaukee, WI.*

Background: Ocular melanoma (OM) has an annual incidence of 3500 to 4000 patients per year, with liver metastases (LM) accounting for the sole or dominant site of metastases in more than 80% of patients. For patients with LM, median survival is reported to be 2 to 7 months, with an estimated 1-year survival of 10%. We present results utilizing liver directed therapy with high-dose melphalan administered via hypertermic isolated hepatic perfusion for patients with unresectable LM from OM. Methods: Between 10/1994 and 6/2012, 105 patients with unresectable LM underwent a 60 min hyperthermic isolated hepatic perfusion (IHP) with melphalan (1-2 mg/kg IBW). IHP included hepatic isolation at laparotomy with inflow via a cannula in the gastroduodenal artery and outflow via a cannula in the isolated retrohepatic vena cava (IVC). Patients were followed for toxicity, radiographic response (WHO criteria), and hepatic progression-free (HPFS) and overall survival (OS). HPFS and OS probabilities were calculated by Kaplan-Meier. Results: There were 51 males and 54 females (mean age: 50 yr [range: 21-76]) with unresectable OM LM (median # metastases: 26 [range: 3-50]; median percent liver replaced by tumor: 22%). There were 3 operative/treatment mortalities (2.9%). There were 62 responses (CR: n=6, PR: 56) in 102 evaluable patients (61%). For all treated patients, median OS was 12 months (range: 1 to 115 months) with 2 and 3-yr survival of 31% and 21%, respectively. Conclusions: IHP with melphalan results in marked tumor regression and prolonged OS in patients with high hepatic tumor burden from metastatic OM. Although this is a non-randomized trial, response to IHP is associated survival superior to that reported with alternative therapies.

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A Comparison Between Perioperative and Post-Operative Chemotherapy after Potentially Curative Hepatic Resection for Metastatic Colorectal Cancer R.L. Araujo,* M. Gonen, N. Kemeny, P.J. Allen, L.H. Blumgart, R.P. DeMatteo, Y. Fong, W.R. Jarnagin, M. D'Angelica. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Additional chemotherapy in patients with resectable colorectal liver metastases (CRLM) likely improves outcomes. Whether to administer chemotherapy before and after (perioperative) or only after liver resection (adjuvant) remains controversial as this question has not been addressed by randomized trials. We analyzed outcomes between these two modalities of treatment. Methods: Patients receiving perioperative or adjuvant chemotherapy were identified from a prospectively maintained CRLM database and studied retrospectively. Only patients who received chemotherapy including oxaliplatin or irinotecan were included. Univariate and Cox regression models were developed to determine factors independently associated with recurrence and death. Results: Between 1998 and 2007, 236 patients (57%) in the adjuvant group and 175 patients (43%) in the perioperative group were compared. The median follow-up was 77 months. The perioperative group were younger (median age 55 versus 61, p<0.001) and had more advanced disease than the adjuvant group. Overall Survival (OS) was not different between the groups, even when adjusted for Clinical Risk Score (CRS - high [3 – 5] p=0.28; and low [0 – 2], p=0.086). Disease free survival (DFS) was worse in the perioperative group, but it was not different when adjusted for CRS (high [p=0.74] and low [p=0.42]). On multivariate analysis, timing of chemotherapy was not associated with DFS (HR=1.22, 95%CI: 0.9-1.64, p=0.2) or OS (HR=1.03, 95%CI: 0.76-1.4, p=0.88). Conclusions: This study suggests that the timing of additional chemotherapy for resectable CRLM is not independently associated with outcomes. Prospective trials addressing this question would require large samples to detect the putative small differences in outcomes.

Characteristics, OS and DFS by timing of chemotherapy	Perioperative	Adjuvant	p value
Synchronous metastasis at diagnosis (%)	74.9	25.9	<0.001
DFI ≤12 months (%)	87.4	48.3	<0.001
Number of lesions > 1 (%)	71.4	52.7	<0.001
Number of Metastases ≥ 5 (%)	21.1	33	0.008
Bilateral metastases (%)	54.9	37.7	0.001
5 y OS (months)	55.8	59.6	0.48
Median OS (months)	72.9	71.5	0.48
5 y DFS (months)	30.7	38.3	0.036
Median DFS (months)	17.2	27.4	0.036

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COX-2 Inhibition with Apricoxib Mediates Response to Chronic Anti-VEGF Therapy A.R. Kirane,[1]* J.E. Toombs,[1] M.T. Dellinger,[1] R.E. Schwarz,[1] F.J. Burrows,[2] R.A. Brekken.[1] *1. UTSW, Dallas, TX; 2. Tragara Pharmaceuticals, San Diego, CA.*

Anti-VEGF therapy with r84 delays PDAC progression in mice; however, chronic therapy and resulting hypoxia is ultimately associated with transition to a mesenchymal phenotype (EMT), increased COX-2 expression, and rapid progression. Here, we evaluate the efficacy of a combination strategy of r84 and apricoxib, a novel COX-2 inhibitor, in preclinical models of pancreatic cancer. In vitro, high expression of COX-2 correlated with high levels of VEGF in conditioned media of PDAC cells. Inhibition of COX-2 suppressed VEGF production transiently but recovered within 24 hours and continued to rise, despite depletion of PGE2. Growth of cells in conditions that induce EMT resulted in an elevation of VEGF that was refractory to apricoxib. The effect of r84, apricoxib, or combination on tumor growth and metastases was determined in SCID mice bearing orthotopic Colo357 xenografts and in genetic model of PDAC (p48Cre/+; KrasG12D;Cdkn2alox/lox). Apricoxib and r84, as single agents, slowed primary tumor growth and significantly suppressed metastatic events. The effect of combination therapy was more potent showing increased efficacy at reducing primary and metastatic tumor burden. Analysis of tumors revealed increased COX-2 expression following r84 as well as an increase in tumor VEGF levels following apricoxib treatment, suggesting a compensatory relationship. Significant shift in the inflammatory milieu was observed with r84 therapy being associated with IL1-β secretion and recruitment of M2 macrophages, MDSCs, and fibroblasts. COX-2 inhibition resulted in predominantly M1 infiltration and increased apoptosis, this was maintained in the combination group. r84 induced hypoxia as a result of angiogenesis inhibition resulted in increased collagen deposition and EMT. Apricoxib therapy as single agent or combination with r84 resulted in a shift toward an epithelial phenotype and reduced collagen deposition. We conclude combination of COX-2 inhibition by apricoxib with anti-VEGF therapy abrogates hypoxia related changes to the microenvironment resulting in potent anti-tumor and anti-metastatic effect. This warrants further evaluation of mechanism and potential as a strategy to augment chemotherapy.

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Improved Post-Operative Survival for Intraductal Growth Subtype of Intrahepatic Cholangiocarcinoma L.L. Dover,* D.A. Dubay, R. Jacob, J.H. Richardson, T.N. Wang. *University of Alabama at Birmingham, Birmingham, AL.*

Intrahepatic cholangiocarcinoma (IC) is an uncommon hepatic neoplasm with an increasing incidence and a poor prognosis. The only known curative option for patients with IC is surgical resection, with reported 5-year survivals between 25%-40%. IC is classified according to the following histologic subtypes: mass forming, periductal infiltrating and intraductal growth. The aim of this study is to measure patient survival following surgical resection for IC. Our hypothesis is that patients with intraductal growth histology have improved survival compared to other histologic subtypes. Methods: A retrospective review was performed identifying all surgical patients treated at our institution for IC. Patients with perihilar and distal cholangiocarcinomas were excluded, as were all patients undergoing aborted or palliative procedures. Survival estimates were quantified using Kaplan Meier curves. Differences between groups were compared with Fisher's exact test and t-test. Results: Between 2004-2011, 37 patients treated with partial hepatectomy for curative intent were identified. The 1, 3 and 5-year overall survivals were 80%, 63% and 51%. There were no significant patient demographic characteristics associated with patient survival: younger age (p=0.08), female gender (p=0.19) and Caucasian race (p=0.65). Similarly, there were no significant tumor pathologic characteristics associated with patient survival: well differentiation (p=0.47), >1mm surgical margin (p=0.47), tumor satellitosis (p=0.44), lymphovascular

invasion (p=0.65) and perineural invasion (p=0.68). Neither adjuvant radiotherapy (p=0.39) nor chemotherapy (p=0.9) was associated with improved survival. Significant differences in patient deaths were observed between histologic subtypes: 11/27 mass forming, 3/3 periductal infiltrating, and 0/8 intraductal growth (p=0.03). Conclusions: Although limited by the small sample size of this rare cancer, this study demonstrates a better than expected overall survival following partial hepatectomy for IC. Recently proposed histologic subtypes were strongly predictive of post-surgical survival, with no deaths observed in the 8 patients with intraductal growth subtype.

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Role of Biliary CEACAM6 as a Biomarker for Cholangiocarcinoma
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INTRODUCTION: Distinguishing bile duct carcinoma from other diagnoses is often difficult using endoscopic or percutaneous techniques. The cell surface protein CEACAM6 is over-expressed in many gastrointestinal cancers and may be selectively elevated in biliary adenocarcinoma. The aim of the present study is to determine if CEACAM6 can be detected in the bile of patients with biliary cancer and can serve as a diagnostic biomarker for cholangiocarcinoma. METHODS: Bile duct and gallbladder bile from patients with benign biliary disease and cholangiocarcinoma (hilar, intrahepatic and distal) was collected at the time of index operation. The concentration of CEACAM6 was quantified by sandwich enzyme-linked immunosorbent assay (ELISA) and correlated to pathologic diagnosis. Diagnostic capability of CEACAM6 was evaluated by Wilcoxon rank-sum, logistic regression, and receiver operating characterisitic (ROC) curve analysis. RESULTS: Bile from 73 patients was analyzed: 40 with benign disease and 33 with cholangiocarcinoma. Patients in the benign cohort were younger, predominantly female, and had lower mean biliary CEACAM6 levels than patients in the malignant cohort (102 ng/ml vs. 239 ng/ml; p=0.0006). Logistic regression analysis determined CEACAM6 to be a positive predictor of extrahepatic but not intrahepatic cholangiocarcinoma (p=0.0015). ROC curve with a CEACAM6 level >22.1 ng/ml was associated with 85% sensitivity, 73% specificity, and a likelihood ratio of 3.15 (AUC 0.82) for extrahepatic cholangiocarcinoma (See Figure). CONCLUSION: CEACAM6 levels in bile can predict patients with extrahepatic cholangiocarcinoma with acceptable accuracy. Further investigation is warranted in a larger cohort of patients prior to clinical application.

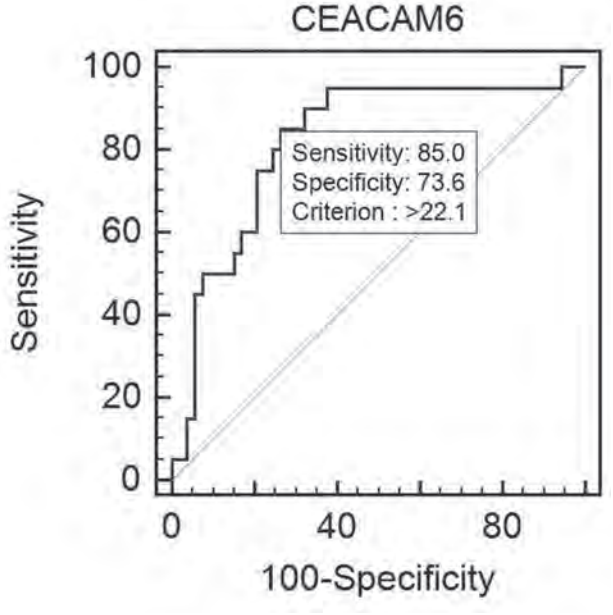

Figure: ROC curve for extrahepatic cholangiocarcinoma and CEACAM6.

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Surgical Resection Combined with Ipilimumab Treatment for Stage IV Melanoma
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Introduction: Ipilimumab is now a FDA-approved treatment for patients with metastatic melanoma. We sought to examine five year disease-specific survival (DSS) from the time of stage IV diagnosis for patients undergoing surgical resection and ipilimumab treatment. Methods: Our cancer center's database was queried for patients who underwent surgical resection and ipilimumab treatment. The 5 year DSS from the time of stage IV diagnosis was calculated from the date of their stage 4 diagnosis. These patients were then divided into two groups— patients who underwent ipilimumab treatment followed by resection or patients who underwent surgical resection followed by ipilimumab treatment. The log-rank test was used to compare the 5 year DSS. Results: 44 patients had surgical resection and ipilimumab treatment with a 5 year DSS of 51% and a median survival of 60 months (CI, 31-66). 25 patients had ipilimumab treatment followed by surgical resection. 5 year DSS was 43%, and median survival was 47 months. 19 patients had surgical resection followed by ipilimumab treatment. 5 year DSS was 65%, and median survival was 60 months. There was no statistically different 5 year DSS between the two groups (p=0.27). Conclusions: This is the first study, to our knowledge, to evaluate 5 year DSS in metastatic melanoma patients who have undergone surgical resection as well as ipilimumab treatment. Although our study has a small cohort, the data suggests that surgical resection and ipilimumab treatment may result in long-term survival in a select group of metastatic melanoma patients. In addition, there does not appear to be a difference in 5 year DSS whether ipilimumab is administered before or after surgery. The role of ipilimumab in combination with surgical resection in metastatic and advanced melanoma needs to be investigated further.

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Iliac Lymph Nodes Metastasis after Ilio-inguinal Radical Lymph Node Dissection for Melanoma
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Background. The management of patients with groin lymph node (LN) metastasis from melanoma is still under discussion. This study sought to investigate: 1) the frequency of positive iliac LN(s), 2) predictors of iliac LNs status, 3) the diagnostic value of pre-operative computed tomography (CT) for characterizing iliac LNs, 4) and Cloquet's LN pathological status for predicting iliac LNs status. Methods. Retrospective data of patients with groin LN metastasis, who have had an ilio-inguinal radical LN dissection (RLND) were analyzed. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) of pre-operative CT scan and Cloquet's LN pathological status were calculated. Results. There were 157 patients who underwent an ilio-inguinal RLND, 81 for a positive sentinel node (SN, 51.6%) and 76 for clinically positive LN metastasis (48.4%). Positive iliac LNs were detected in 42 patients (26.7%); 14 were SN-positive (17.3%) and 28 had clinically positive LN (36.8%, P=0.007). The number of positive inguinal LN(s) was the only independent predictor of deep LN involvement [odds ratio (OR) 1.42, 95%CI 1.15-1.74, P<0.001] and LN tumor burden achieved a borderline non-significance (OR 0.42, 95%CI 0.18-1.003, P=0.051). According to a receiver operating characteristics (ROC) curve, model's accuracy was 0.723 (P<0.001). Accuracy, sensitivity, specificity, PPV and NPV of CT scan (available for 108 patients) in identifying iliac LNs metastasis were 58.3%, 48.6%, 63.4%, 40.9% and 70.3% in all the patients, 74.4%, 27.3%, 90.6%, 50.0% and 78.4% in patients with micrometastasis and 47.7%, 57.7%, 41.0%, 39.5% and 59.4% in patients with clinically positive LNs, respectively. Accuracy, sensitivity, specificity, PPV and NPV of Coquet's LN (available for 61 patients) were 78.7%, 41.2%, 93.2%, 70.0% and 80.4%, respectively. Conclusions. There was a relatively high frequency of iliac LNs metastasis (17.3% and 36.8% for micro- and macro-metastasis, respectively). The number of positive inguinal LN(s) was the only predictor of iliac LN metastasis. Pre-operative CT scan and pathological examination of Cloquet's LN had poor value for guiding extension of surgery.

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Detection of Circulating Melanoma Cells in the Blood of Melanoma Patients: Feasibility and Preliminary Significance C.L. Roland,* M.I. Ross, C.S. Hall, B. Laubacher, A. Lucci. *MD Anderson Cancer Center, Houston, TX.*

Introduction: Significant prognostic heterogeneity exists within each of the substages of melanoma, therefore novel prognostic factors are needed. One potential factor is the presence of circulating melanoma cells (CMC). While limited available data suggests prognostic significance for CMCs, there is a need for a sensitive, reproducible, and standardized identification technique. Using a semi-automated technology, we sought to determine whether CMCs could be identified and if their presence correlated with advancing stage of disease. Methods: CMCs were detected from the peripheral blood (7.5cc) of patients with stage I-IV melanoma (n=62) using the CellSearchTM system (Veridex, Raritan NJ USA). Patients with Breslow thickness < 0.75mm and no unfavorable features (mitotic figures, ulceration) were excluded. CD146+ cells were immunomagnetically enriched and CMCs were identified as CD146+, HMW-MAA+, CD45-, and CD34-. The presence of CMCs was correlated with known prognostic factors in melanoma. Results: Median age was 54 years. One or more CMCs was detected in 45% of all patients, varying with stage of disease (Stages I /II, III, and IV: 35%, 48%, and 80%, respectively; p=0.03, for stage I/II vs stage IV). Of these patients, 61% had one CMC, 29% had two CMC and 10% had three or more CMCs identified. The presence of CMCs in the blood was associated with histologic subtype, particularly in patients with Stage I /II disease (superficial spreading 18% vs. other subtypes 78%; p=0.003). There was a non-significant trend toward increased CMCs in patients with primary tumors with ≥ 2 mitotic figures. Conclusion: Using this semi-automated technique, CMCs can be identified in a significant number of melanoma patients and their presence correlates with advancing stage and other relevant primary tumor factors. These data support further study with longer follow-up and longitudinal/serial time points to better assess the significance of detecting CMCs in melanoma patients.

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Unique Genes in Tumor-Positive Sentinel Lymph Nodes Associated with Non-Sentinel Lymph Node Metastases in Melanoma M.E. Egger,[1]* D. Xiao,[1] H. Hao,[1] J. Pan,[2] S.N. Rai,[2] A.C. Cambon,[2] S.J. Waigel,[2] W. Zacharias,[2] K.M. McMasters.[1] *1. University of Louisville - Hiram C. Polk, Jr, MD Department of Surgery, Louisville, KY; 2. University of Louisville, Louisville, KY.*

Introduction: Currently, melanoma patients with a tumor-positive sentinel lymph node (SLN) biopsy undergo completion lymphadenectomy of the involved nodal basin, but only 10-20% of these patients will have metastases to the remaining lymph nodes (non-SLN). Clinical and pathologic factors of the primary tumor and SLN are unreliable predictors of non-SLN metastases. We hypothesized that an analysis of differentially expressed genes in the SLNs may identify those patients with an increased risk of non-SLN metastases. Methods: Total RNA was collected from tumor-positive SLNs in patients enrolled in a multi-center randomized prospective clinical trial. We compared SLN samples in patients who had tumor-positive non-SLNs after completion lymphadenectomy to controls without non-SLN metastases after lymphadenectomy. Affymetrix GeneChip HGU-133 Plus 2.0 Array was used for microarray analysis comparing the cases and controls. Differentially expressed genes were also identified using a multivariate regression model controlling for gender, age, ulceration, and Breslow thickness (BT). Quantitative reverse-transcriptase polymerase chain reaction (PCR) assays were performed to confirm differential expression. Results: A 1:10 case:control series was established with 7 positive non-SLN cases matched with 70 negative non-SLN controls. The cases and controls were similar with regards to clinicopathologic factors such as gender, primary tumor site, age, ulceration, and BT ($p > 0.05$). By microarray analysis for comparing two groups, 8 unique genes were differentially expressed in the SLNs between the cases and controls ($p < 0.05$). Subsequent analysis by regression modeling that included age, gender, BT, and ulceration identified 37 differentially expressed genes at a significance level of $p < 0.01$ (25 genes with $p < 0.005$). Preliminary quantitative PCR analysis confirmed altered gene expression in the tripartite motif (TRIM) protein family and genes in the ATP binding-cassette family. Conclusions: Unique gene expression signatures in tumor-positive SLNs may identify patients at greater risk for non-SLN metastases.

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S-100B: A Stronger Prognostic Biomarker than LDH in Stage IIIB-C Melanoma K.P. Wevers,* S. Kruijff, M.J. Speijers, E. Bastiaannet, A.C. Muller Kobold, H.J. Hoekstra. *UMCG Groningen, Groningen, Netherlands.*

Introduction: In melanoma patients with nodal macrometastases, distinction between good and poor prognosis is based on the presence of primary melanoma ulceration or metastatic involvement of 4 or more lymph nodes in the 7th AJCC classification. We hypothesized that biomarkers would increase the accurateness of staging in these patients. The aim was to assess and compare the prognostic impact of biomarkers S-100B and LDH and to determine the best timing of their measurement in stage IIIB-C melanoma. Methods: A total of 119 patients underwent therapeutic lymph node dissection (TLND) for nodal macrometastases with serum S-100B and LDH level measurements preoperatively. In 75 of them, S-100B and LDH was also measured on postoperative days 1 and 2. S-100B and LDH levels on days 0, 1, and 2 were compared for their association with disease-free survival (DFS) and disease-specific survival (DSS). Results: At a median follow-up of 17 (range 1-89) months, S-100B levels at all time points were associated with DFS. In multivariable analysis, preoperative S-100B and S-100B measured on day 2 showed the strongest association with DFS (HR=2.55, p=0.007 and HR=3.80, p=0.01). For DSS, the preoperative S-100B level was the strongest independent predictor (HR=2.81, p=0.01). LDH measurements showed a significant association with DSS in univariate analysis, only when measured preoperatively (HR=2.46, p=0.01). In multivariable analysis, LDH measurement was not associated with melanoma prognosis. (Table 1) The 5-year DFS was 37.8% and 5-year DSS was 47.4% for patients with normal preoperative S-100B levels, which was significantly better than the 5-year DFS of 6.6% and the 5-year DSS of 28.3% for patients with elevated S-100B levels. Some differences in survival percentages were seen between patients with normal and elevated preoperative LDH levels. In patients with normal preoperative LDH levels 5-year DFS was 27.1% and 5-year DSS was 48.0% compared to 18.6% and 20.5% for patients with elevated LDH levels. Conclusion: The S-100B level measured preoperatively is, in contrast to LDH, one of the most important independent predictors of melanoma prognosis in patients undergoing TLND for nodal macrometastases.

Table 1. Biomarkers LDH and S-100B levels on different time points and their association with melanoma prognosis in 75 patients

Characteristic	n	(%)	DFS Univariate HR (p)	DFS Multivariable[a] HR (p)	DSS Univariate HR (p)	DSS Multivariable[b] HR (p)
Preoperative LDH						
Normal	59	(78.7)	1		1	1
Elevated	16	(21.3)	1.61 (0.14)		**2.46 (0.01)**	1.48 (0.33)
LDH day 1						
Normal	71	(94.7)	1		1	
Elevated	4	(5.3)	1.33 (0.83)		2.04 (0.24)	
LDH day 2						
Normal	69	(92.0)	1		1	
Elevated	6	(8.0)	1.20 (0.72)		1.85 (0.25)	
Perioperative LDH change						
Became normal	12	(16.0)	1		1	1
Remained elevated	4	(5.3)	0.88 (0.84)		1.02 (0.98)	1.30 (0.75)
Became elevated	2	(2.7)	0.62 (0.66)		0.71 (0.75)	1.10 (0.93)
Remained normal	57	(76.0)	0.16 (0.60)		**0.40 (0.02)**	0.73 (0.47)
Preoperative S-100B						
Normal	48	(64.0)	1	1	1	1
Elevated	27	(36.0)	**3.08 (<0.001)**	**2.55 (0.007)**	**3.33 (0.001)**	**2.81 (0.01)**
S-100B day 1						
Normal	61	(81.3)	1	1	1	
Elevated	14	(18.7)	**2.66 (0.003)**	**2.45 (0.01)**	1.63 (0.23)	
S-100B day 2						
Normal	69	(90.7)	1	1	1	1
Elevated	7	(9.3)	**5.94 (<0.001)**	**3.80 (0.01)**	**3.93 (0.005)**	**3.76 (0.04)**
Perioperative S-100B change						
Became normal	22	(29.3)	1	1	1	1
Remained elevated	5	(6.7)	**5.69 (0.001)**	**3.39 (0.04)**	1.82 (0.31)	2.40 (0.23)
Became elevated	2	(2.7)	1.08 (0.94)	1.32 (0.80)	2.07 (0.49)	3.28 (0.30)
Remained normal	46	(61.3)	**0.37 (0.002)**	**0.42 (0.02)**	**0.32 (0.002)**	**0.35 (0.02)**

a Hazard ratio for DFS adjusted for presence of ulceration, LN ratio, and extranodal growth.

b Hazard ratio for DSS adjusted for sex, presence of ulceration, LN ratio, and extranodal growth.

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LDH, lactate dehydrogenase.

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MicroRNA Profiling Classifies Problematic Melanocytic Lesions S.E. Martin del Campo,[1]* V.P. Grignol,[2] J.R. Clark,[3] S.B. Peters,[1] W.E. Carson.[1] *1. The Ohio State University, Columbus, OH; 2. Medical College of Wisconsin, Milwaukee, WI; 3. Wright State University, Dayton, OH.*

Introduction: MicroRNAs (miRs) are small, noncoding RNAs that inhibit gene expression and regulate many cellular processes. We have previously shown a distinct miR expression pattern in malignant melanoma tumors. However, the malignant potentials of some melanocytic lesions are difficult to predict and create a therapeutic dilemma. Undertreatment of lesions thought to be benign can adversely impact survival. Conversely, overtreatment of lesions thought to be malignant can result in unnecessary morbidity from surgery or adjuvant therapy. We hypothesized that characterization of miR expression in atypical Spitz tumors would result in a molecular profile that identifies lesions with high malignant potential, requiring more aggressive therapy. Methods: RNA extraction was performed on formalin fixed, paraffin embedded tissue samples of benign nevi (n=19), benign Spitz tumors (n=19), atypical Spitz tumors (n=20), and spitzoid melanomas (n=6). Based on previous microarray data, the following 12 miRs were analyzed: let-7a, miR-17-5p, miR-21, miR-22, miR-23b, miR-34a, miR-125b, miR-148b, miR-150, miR-155, miR-200c, and miR-211. miR expression was evaluated by real-time PCR Taqman assays, using RNU48 as an endogenous control. Results: In general, Spitz lesions were characterized by decreased expression of miR-125b and miR-211. For example, benign Spitz tumors exhibited 2-fold and 3-fold decreases in miR-125b and miR-211 compared to benign nevi, respectively ($p<0.05$). A comparison of spitzoid melanomas to benign nevi revealed 3 to 7-fold over-expression of miR-22, miR-34a, miR-150 and miR-155 in the malignant primaries ($p<0.05$). Importantly, spitzoid melanomas exhibited a 4-fold increase in levels of miR-150 and a 7-fold increase in levels of miR-155 as compared to a panel of atypical Spitz tumors ($p<0.01$). Therefore, spitzoid melanomas can be differentiated from atypical Spitz tumors and benign nevi by virtue of their increased expression of miR-150 and miR-155. Conclusions: miR expression profiles can be used to characterize problematic Spitz tumors as benign or malignant and provide guidance to clinicians in the selection of surgical procedures and adjuvant therapies.

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Tumor Heterogeneity in Metastatic Melanoma Patients with BRAF/NRAS Mutations C.H. Yoon,[1]* J. Le,[1] N. Ibrahim,[2] J. Gold,[1] M.M. Bertagnolli,[2] F.S. Hodi.[2] *1. Surgery, Surgical Oncology, Brigham and Women's Hospital, Boston, MA; 2. Dana Farber Cancer Institute, Boston, MA.*

Introduction: Targeted therapy with Braf inhibitors in metastatic melanoma has shown remarkable initial effectiveness in treatment of metastatic disease in patients with Braf mutations. However, the response to Braf inhibition is frequently short-lived. Resistance mechanisms include activation or over-expression of parallel signaling pathways or by support from neighboring non-melanoma cells. Methods: To study the potential heterogeneity in metastatic melanoma, we generated cell lines from fresh tumor tissue of melanoma patients using standard cell procurement and isolation methods. These early-passage cells were evaluated using immunofluorescence and genomic mutational analysis. Results: Between March 2010 and July 2012, fresh surgical samples from 30 patients were processed to generate viable cell lines for in vitro culture in 36 attempts. 16 of these patients had Braf or Nras mutations confirmed by genomic analysis of fixed tumor samples. We were able confirm the genetic mutations in Braf or Nras from 9 tumor sample generated cell lines by genomic sequencing. Remaining7 tumor samples generated cells that were wild-type for both Braf and Nras. In at least 4 of these 9 tumor samples, we found a mixture of atypical cells that included at least 2 phenotypically distinct subsets: these were separated to cells that have Braf or Nras mutations and cells that were wild-type in both genes. All of the wild-type cell lines from patients with Braf or Nras mutations were atypical and immortalized. They showed similar but not identical phenotypic and growth characteristics. These cells survived selection against fibroblasts in culture. Immunofluorescence studies of these cells in culture showed varying expression of S100, MelanA, and HMB-45. Furthermore, these cells showed expression of CD166, Nestin, and/or ABCB5. Conclusions: These results demonstrate significant heterogeneity of cell populations within metastatic melanoma and show the presence of atypical cells that are distinct from mutation-bearing melanoma cells.

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Molecular Characterization and Patient Outcome of Unknown Primary Melanoma with Nodal Metastases A. Gos,[7] A. Van Akkooi,[2] C. Robert,[3] M. Jurkowska,[4] S. Koljenović,[9] N. Kamsukom,[3] W. Michej,[8] A. Jeziorski,[5] C. Voit,[6] H. Kosela,[1]* P. Pluta,[5] J. Siedlecki,[7] A. Eggermont,[10] P. Rutkowski.[1] *1. Department of Soft Tissue/Bone Sarcoma and Melanoma Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; 2. Erasmus University Medical Center - Daniel den Hoed Cancer Center - Department of Surgical Oncology, Rotterdam, Netherlands; 3. Institute Gustave Roussy Dermatology Department, Villejuif Paris Sud, France; 4. Institute of Rheumatology, Warsaw, Poland; 5. Department of Surgical Oncology Medical University of Lodz, Lodz, Poland; 6. Klinik für Dermatologie, Venerologie und Allergologie, Charite - University Medicine Berlin, Berlin, Germany; 7. Department of Molecular Biology; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; 8. Departament of Pathology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; 9. Department of Pathology Erasmus University Medical Centre – Daniel den Hoed Cancer Centre,, Rotterdam, Netherlands; 10. Cancer Institute Gustave Roussy, Villejuif Paris Sud, France.*

Purpose: Melanoma of unknown primary site (MUP) is not completely understood entity with nodal metastases as the most common clinical manifestation. The aim of this multicentric study was to assess frequency and type of oncogenic BRAF/NRAS/KIT mutations in MUP with clinically detected nodal metastases in relation to clinicopathologic features and outcome. Methods: We analyzed series of 95 MUP patients (median age 56 years) after therapeutic lymphadenectomy - LND (period: 1992-2010, 35 – axillary, 44 - inguinal, 16 – cervical) not treated with BRAF inhibitors and performed molecular characterization of BRAF/NRAS/KIT mutational status in nodal metastases using direct sequencing of respective coding sequences. Median follow-up time was 51 months. Results: BRAF mutations were detected in 55 (58%) cases (51 V600E - 93%, 4 others - 7%), and mutually exclusive NRAS mutations in 10 (10.5%) cases (6 Q61K, 2 Q61H, 1 Q61R, 1 Q13R). We have not detected any mutations in KIT or PI3K. 5-year overall survival (OS) was 34%, median – 24 months (from date of lymph node dissection). We have not found correlation between mutational status (BRAF or NRAS) and OS (calculated from date of LND and primary tumor excision), however for BRAF mutated-melanomas we have observed significantly shorter disease-free survival (DFS) as compared to patients with wild-type melanoma ($p=0.02$; 5-year DFS 31% vs. 18%, respectively). The most important factor influencing OS and DFS was number of metastatic lymph nodes>1 ($p=0.01$). Conclusion: Our large comprehensive study on molecular characterization of MUP with nodal metastases showed that MUPs have similar molecular features as sporadic non-chronic-sun-damaged melanomas. BRAF mutational status has negative impact on DFS in this group of patients, NRAS status is not prognostic marker, what may have potential implications for adjuvant therapy.

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Sentinel Lymph Node Biopsy (SLNB) is Associated with Improved Survival in Merkel Cell Carcinoma S.D. Kachare,* N.A. Vohra, J. Wong, E.E. Zervos, T.L. Fitzgerald. *Surgical Oncology, East Carolina University - Brody School of Medicine, Greenville, NC.*

Introduction: Well-designed, randomized clinical trials have defined the utility of SLNB in melanoma and breast cancer, yet no such data exists for Merkel Cell Carcinoma (MCC). In order to better define the staging and therapeutic value of SLNB for MCC, we compared patients who underwent wide local excision (WLE) with SLNB to WLE alone (observation) in a large cancer registry. Method: All patients undergoing surgery for MCC between 1988 -2009 were identified in the SEER tumor registry. In order to construct the two study groups, SLNB vs. observation, patients were excluded if they had metastatic disease, incomplete staging, or clinically

positive lymph nodes. Results: A total of 5,390 patients were identified, 1,636 met inclusion criteria (SLNB 556 and Observation 1,080). The median age was 77 years(y). The population was 94.7% white and 59.4% male. A total of 64.1% of patients had T1-stage tumors and 45.4% underwent radiotherapy. SLNB was positive in 24.1%. On univariate analysis, patients undergoing SLNB were more likely to be younger (73y vs. 80y, p<0.001), T1 (68.4% vs. 61.9%, p= 0.01) and treated with radiotherapy (55.9% vs. 40%, p<0.001). Age (p < 0.001) and T1 status (p= 0.02) maintained significance on logistic regression. The overall median survival was 48 months (mo.). In the SLNB group, a negative SLNB was associated with improved survival, 107 vs. 40 mo., p<0.001. Univariate survival analysis demonstrated increased survival for SLNB vs. observation (89 vs. 39 mo., p < 0.001), female gender (72 vs. 42 mo., p<0.001), radiotherapy (57 vs. 43 mo., p < 0.001), lower T-stage (p < 0.001) and non-AA race (p= 0.04). On multivariate Cox regression, diminished survival was noted for observation (RR 1.47, 95%CI 1.24-1.76, p<0.001), male gender (RR 1.75, 95%CI 1.50-2.01, p<0.001), omission of radiation (RR 1.22, 95%CI 1.04-1.39, p0.006), higher T- stage, and African Americans (RR: 2.40, 95%CI 1.24-4.44, p=0.01). Conclusion: SLNB for MCC provides prognostic information and is associated with a significant survival advantage.

Survey responses to questions of payment for 1 year of life under various circumstances

QUESTION	PAYMENT AMOUNTS (US$)	NUMBER OF RESPONDENTS (%)
Patients pay out of pocket for 1 YEAR of THEIR OWN life in a POTENTIALLY CURABLE setting		
	$0-49,999	92 (29.6)
	$50,000-99,999	32 (10.3)
	$100,000-199,999	21 (6.8)
	$200,000-499,999	19 (6.1)
	$500,000-1,000,000	9 (2.9)
	No limit	138 (44.4)
	No response	24
Insurance pay for 1 YEAR of THEIR OWN life in a POTENTIALLY CURABLE setting		
	$0-49,999	23 (7.3)
	$50,000-99,999	34 (10.8)
	$100,000-199,999	27 (8.6)
	$200,000-499,999	24 (7.6)
	$500,000-1,000,000	28 (8.9)
	No limit	178 (56.7)
	No response	21
Insurance pay for 1 YEAR of A STRANGER'S life in a POTENTIALLY CURABLE setting		
	$0-49,999	25 (8.1)
	$50,000-99,999	35 (11.3)
	$100,000-199,999	25 (8.1)
	$200,000-499,999	24 (7.7)
	$500,000-1,000,000	28 (9.0)
	No limit	173 (55.8)
	No response	25

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Patient Attitudes About the Cost of Cancer Care: Expectations and Realities in the Current Health Care Climate D.E. Abbott,[1]* D. Hanseman,[1] S.A. Ahmad,[1] C.D. Tzeng,[2] V. Sohn,[2] S.A. Curley.[2] *1. Surgery, University of Cincinnati, Cincinnati, OH; 2. The University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: Health care costs are rising at an unsustainable rate. While recognized by many policy experts and some politicians, effective reform has been absent or prohibitively slow, in part due to patient expectations and demands. To understand patient and public attitudes about the cost of cancer care, we solicited cancer patients and their friends or family for opinions about cost of care and analyzed their responses based on demographic differences. Methods: A 20-question survey was sent to patients who received care from the Department of Surgical Oncology at our institution. The survey questions were related to individual demographics and opinions about costs of care in a variety of settings and who is primarily responsible for these costs. Responses were compared between demographic groups. Results: There were 335 respondents. A majority of respondents were female (57.9%), over 50 years old (74%) and Caucasian (81.5%). 55.2% of respondents had a combined annual income of less than $100,000. In a curable setting, 44.4% and 56.7% of respondents believed there should be no limit to the amount the individual or insurance company should pay for 1 year of life, respectively. However, respondents did believe that less should be spent on care in an incurable setting. There were no differences between patients and family/friends (p=.95) or by gender (p=.33), age group (p=.89) or ethnicity (p=.20), with regards to spending for curable versus incurable scenarios. Non-Caucasians were significantly more likely to believe that more should be spent on themselves than for a stranger; 7.1% vs 2.0% (p=.03). Conclusions: The amount that respondents believed should be spent on cancer care far exceeded commonly accepted (or feasible) per patient spending in the United States. To contain health care costs, there will need to be increased patient and public education as we align the attitudes of individual patients, the public, and policy makers.

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Clinical Impact of Real Time Reporting Using the Commission on Cancer's Rapid Quality Reporting System: Is It Worthwhile? S. Kumar,* M. Betrus, J. Fitzgerald, C. Rinaldo, K. Delgado, S.B. Edge. *Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY.*

INTRODUCTION: Quality of care measures are associated with improved cancer outcomes. Deviations can go undetected or are discovered late, allowing little to no time for effective intervention. The aim of this study was to assess the clinical impact of the Commission on Cancer (CoC)'s Rapid Quality Reporting System (RQRS) on delivery of cancer care. METHODS: Using the CoC's RQRS program and Cancer Registry software, patients' records were flagged when approaching deviation from pre-determined quality measures. Starting at 90 days prior to an "alert" becoming a "lapse," a monthly report was generating, triggering: 1. cancer registry chart review; 2. attempt to complete information; 3. provider contact. A questionnaire was performed of both registrars and cancer providers. RESULTS: From January 2011 to September 2012, 280 alerts were generated for breast quality measures and 8 alerts for colon/rectal quality measures. The dashboard figured below describes the performance measures assessed. A single patient often generated multiple alerts. The first review resolved 228 of the alerts (81.4%) as internal documentation demonstrated either receipt or refusal of recommended therapy. 57 alerts went on to an actual lapse in treatment. 42% of these were removed from the list after further review, and 15 patients (generating 17 lapses and 33 alerts) demonstrated an actual lapse in care. Four of the 17 lapses (23.5%) should have been removed from the list due to refusal of care, 3 patients were truly lost to follow up and 10 patients (58.8%) ultimately received appropriate cancer care, although untimely. Reasons for delay included medical comorbidities, incarceration, and relocation. Since its pilot in 2008, registars note increased efficiency with updating documentation and improved timely abstraction. Providers noted improved teamwork and less worry regarding patients lost to followup. CONCLUSION: The CoC's RQRS is an easy-to-use prospective and proactive tool for identifying and improving documentation of cancer care. Few patients lapse in care, however the program offers a safety mechanism for providers to successfully identify approaching lapses.

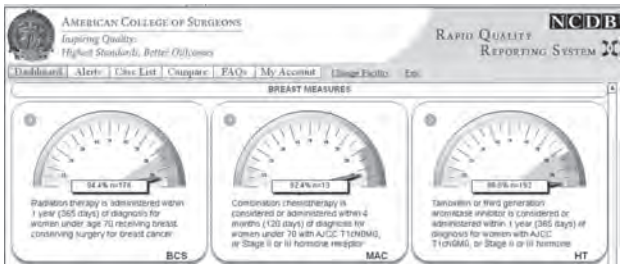

Figure 1: Dashboard showing clinical outcomes for breast quality measures as provided by the RQRS

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Do Hospitals Need Cancer-specific Quality Comparisons? Assessment of Performance for Cancer Versus Non-cancer Surgery

J.L. Paruch,* R.P. Merkow, A. Stewart, M.H. Ju, D. Winchester, C.Y. Ko, K.Y. Bilimoria. *American College of Surgeons, Chicago, IL.*

INTRODUCTION: Surgical quality measurement programs largely report outcomes for all patients and adjust for indication (e.g., cancer vs. diverticulitis). However, it is unknown if hospital performance differs for cancer vs. non-cancer indication, and if so, whether performance is driven primarily by one group. Our objectives were to determine (1) if hospital 30-day outcome performance varies by cancer vs. non-cancer indication and (2) which indication is more closely associated with overall hospital performance. METHODS: Using ACS NSQIP data, we identified patients undergoing colon, rectum or pancreas resections (2007-11). Hierarchical models were developed and hospital quality rankings were separately generated based on (1) all, (2) non-cancer and (3) cancer-only indications. Differences in hospital performance by indication category were assessed by change in rank and agreement statistics. RESULTS: Cancer cases made up 48% of colon (n=93,846), 48% of rectum (n=13,477) and 79% of pancreas (n=14,570) resections. Patients without cancer were older, had higher ASA class and underwent more emergency cases. Hospital rankings for cancer vs. non-cancer indication were considerably different (median change in rank: 53 for colon, 70 for rectum, 66 for pancreas), as was outlier status agreement (K=0.187 for colon, 0.134 for rectum, 0.093 for pancreas; Table 1). When the all-indication model was separately compared to the non-cancer and cancer-only models, agreement in hospital rank was similar for colon (all vs. non-cancer: r=0.87, K =0.656;, all vs. cancer: r=0.81, K =0.450) and rectum (all vs. non-cancer: r=0.77, K =0.594; all vs. cancer: r=0.78, K =0.492), whereas for pancreas the all-indication model was more similar to the cancer model (all vs. non-cancer: r=0.50, K =0.230;, all vs. cancer: r=0.91, K =0.826). CONCLUSIONS: Hospital rankings differ for cancer and non-cancer operations. Overall performance for colon and rectal surgery is driven by both groups, while pancreas performance is driven primarily by cancer cases. Hospitals interested in the quality of their cancer care would benefit from independently examining their cancer surgery outcomes.

	Rank Based on Cancer Indication			
Colon	Top Performers	Middle	Low Performers	Total
Rank Based on Non-cancer Indication				
Top Performers	20	30	11	*61*
Middle	32	124	28	*184*
Low Performers	9	30	22	*61*
	61	*184*	*61*	*306*
Rectum				
Rank Based on Non-cancer Indication				
Top Performers	15	24	14	*53*
Middle	28	94	28	*150*
Low Performers	13	28	11	*52*
	56	*146*	*53*	*255*
Pancreas				
Rank Based on Non-cancer Indication				
Top Performers	16	30	13	*59*
Middle	23	93	26	*142*
Low Performers	12	30	12	*54*
	51	*153*	*51*	*255*

Table1. Changes in Hospital Ranking for 30-Day Mortality or Serious Complication. "Top performers" indicates statistical outlier or top 10%. "Low performers" indicates statistical outlier or bottom 10%.

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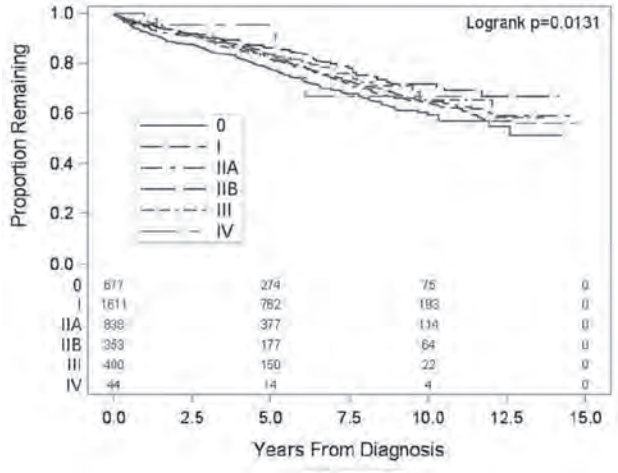
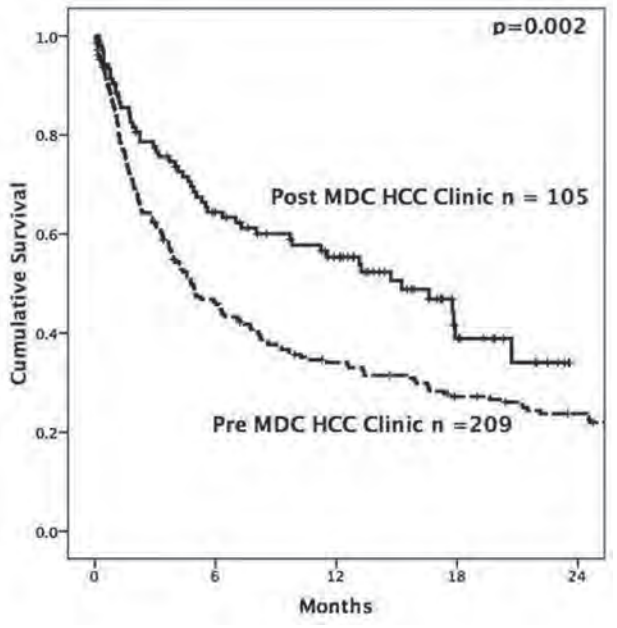
Fostering Coordinated Survivorship Care in Breast Cancer: Who is "Lost to Follow-up"? M. Kukar,* N. Watroba, A. Miller, S. Kumar, S.B. Edge. *Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: Providing long term care for the ever increasing number of breast cancer (BC) survivors is stretching resources at many cancer centers, and they may have equivalent outcomes through care with primary care providers. Many patients triage themselves to care sources other than the oncologist, and are considered "lost to follow-up" (LTFU) by the oncologist. Identifying these patients may help plan for optimal survivorship programs and transfer plans and practices. This study examined patient and tumor characteristics associated with self-transfer of care outside one large cancer center. Methods: Cancer program database records on women with incident BC diagnosed between 7/1/1997 and 3/31/2010 were linked to hospital billing data to identify the date and provider of last follow-up at the center. A patient was classified as LTFU if she had a no visit at the cancer center from 4/1/2008 – 3/31/2012 (2 years), or no visit within 2 yrs of death if she had died. Patient, tumor and treatment characteristics were examined in a multivariate proportional hazards model to identify factors associated with being LTFU. The proportion LTFU was examined by Kaplan Meir plot with cases censured for death. Results: Among 3,924 women with incident BC, 858 (21.9%) were LTFU. At 5 and 10 yrs, 18% and 36% were LTFU, respectively. On univariate analysis, factors significantly associated with being LTFU were higher age, longer travel distance from home to the center, lower TNM stage, no adjuvant therapy and last visit by a surgical vs. medical oncology doctor. Factors not associated with being LTFU were race/ethnicity and type of surgery. Factors independently associated with LTFU were age at diagnosis (unit increase 1.01 / year age), Stage IIA (HR 1.30, p=.02), road distance to the center 40 – 99 miles vs. < 40 miles (HR 1.65, p<.01) and last visit in medical oncology vs. surgical oncology (HR 0.32 p<.01). Conclusions: Many patients with BC self-triage from oncology follow-up with 18% being LTFU at the center by 5 years after diagnosis. Programs to assist patients with care transfer are critical to assure coordinated transfer to other providers and improve continuity of care.



Proportion Lost to Follow-up by Stage



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Establishment of Multidisciplinary (MDC) Hepatocellular Carcinoma (HCC) Clinic is Associated with Better Clinical Outcome
K.T. Ostapoff, A. Singal, J. Marrero, R.E. Schwarz, G.C. Balch, J.C. Mansour, A.C. Yopp.* *Surgical Oncology, UT Southwestern Medical Center, Dallas, TX.*

Multidisciplinary clinics are prevalent in the management of cancer. However, there is a lack of data demonstrating improved outcomes. The variability of liver- and tumor-specific factors in HCC mandates multimodal therapy. The aimof this study was to evaluate the impact of establishing a MDC HCC clinic. Methods: A MDC HCC clinic consisting of surgeons, hepatologists, oncologists, and radiologists was established October 2010. After this date, any patient with HCC or suspected HCC (any liver mass on radiology or elevated AFP) was evaluated in the MDC clinic. We conducted a retrospective review of a prospective HCC database to identify patients diagnosed in the year following and three years prior to initiation of the MDC clinic. Demographics, tumor characteristics, treatment regimens, and survival were compared between the two groups of patients with one-way ANOVA and Chi-squared tests. Survival curves were generated using Kaplan-Meier with log rank test. Results:105 patients were identified in the year prior to the MDC clinic and 209 patients in the 3 previous years. There was no difference in gender, race/ethnicity, etiology of cirrhosis, or Child-Pugh stage between the groups. Patients diagnosed after the MDC clinic were found at earlier tumor stages by AJCC and BCLC classification (p=0.001 and p=0.003, respectively). More post-clinic patients received treatment (56% vs. 44%, p=0.04), and time-to-treatment was shorter (2.2 vs. 4.6 months, p=0.001) than those diagnosed prior to the MDC clinic. Median survival of patients diagnosed after the MDC clinic was significantly longer than those seen during the 3 prior years (15.2 vs. 4.7 months, p=0.002). This difference in survival persisted when patients who were lost to follow-up or died within one month of HCC diagnosis were excluded (17.7 vs. 7.0 months, p=0.004). Survival after excluding BCLC D patients was also longer in the post-clinic period (one year survival, 64% vs. 47%, p=0.001). Conclusions: Formation of a MDC HCC clinic is associated with improved survival, most likely due to more streamlined care resulting in HCC diagnosis at earlier tumor stage and shorter time to treatment.

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Elevated C-Reactive Protein as a Predictor of Patient Outcomes Following Palliative Surgery
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Introduction: There are limited outcomes data guiding optimal surgical decision-making and informed consent for palliative procedures. Decreased performance status, poor nutrition, significant weight loss, and no prior cancer therapy have been associated with worse patient outcomes; however, patient selection continues be challenging for even the most experienced surgeons. Several reports showed an association between CRP and major primary oncologic surgical outcomes; we analyzed CRP in palliative operations. Methods: Procedures to palliate symptoms of advanced cancer were identified from a prospective palliative surgery database. Patients with a recorded preoperative serum CRP (normal 0-8 mg/L) were identified and observed for at least 90 days or until death. Results: 50 patients were identified who underwent an elective palliative procedure performed from July 2008 to June 2012. Operations were performed for gastrointestinal obstruction (35%), loco-regional control of tumor-related symptoms such as pain (28%) or bleeding (7%), and other (30%). Patient-reported symptom resolution or improvement was noted following 37 of 50 procedures (74%). Palliative procedures were associated with 42% morbidity and 10% mortality at 30 days post-op. CRP (range 1-144 mg/L, median 9.6 mg/L) was elevated in 27 patients and independently associated with developing a high-grade complication (p=0.008). Median survival was significantly decreased in patients with an elevated CRP (median 167 days versus 592 days, p=0.014). On multivariate analysis, only elevated preoperative CRP ($p<0.017$) was associated with worse overall survival; NCI fatigue score ≥1 (p=0.08) and ECOG performance status ≥2 (p=0.47) were not associated. Conclusions: Highly-selected patients with advanced cancer can be afforded symptom improvement and the opportunity for improved quality of life following palliative procedures. Elevated preoperative CRP may help identify patients who are less likely to realize the benefits of a palliative operation. Systemic inflammation, reflected by elevated CRP, may be associated with higher risk of postoperative complications and poorer overall survival in advanced cancer patients.

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A Multi-Center Double-Blind, Placebo-Controlled Study on the Effect of a Peripherally Acting μ-Opioid Receptor Antagonist, Alvimopan, on Intestinal Cancer Surgery Patients in an Enhanced Recovery Pathway M.J. Ott,* R. Moesinger, M. Peters, J. Zhang, J. Prochazka, G. Bullock, K. Robins, L. Archibald. *Intermountain Healthcare, Salt Lake City, UT.*

Background. The aim of this study was to determine the effect of a peripherally acting μ-opioid receptor antagonist, alvimopan, on the length of stay (LOS) and treatment cost in patients undergoing elective bowel resections for cancer who already had decreased LOS through participation in an established fast-track enhanced recovery after surgery protocol. Patients and Methods. A multi-center prospective double-blind, placebo-controlled study of 246 patients undergoing elective small bowel and colonic resections was conducted. This is a subset analysis of 77 patients with a primary diagnosis of small bowel or colonic malignancy. Eight institutions ranging from small community hospitals to a tertiary care center participated in this study from 2010 to 2012. Statistical analysis was done using non-parametric methodology. Results. Of the 77 patients, 54 (70%) underwent laparoscopic resections and 23 (30%) underwent open resections and were equally distributed between placebo and alvimopan groups (p = 0.5129). Patients had APDRG severity of illness ranging from 1 (27, 35%), 2 (44, 57%), 3 (5, 6.5%), and 4 (1, 1%). The mean/median length of stay for the 42 patients in the placebo arm was 5.9/4.11 days (1.94 - 30.18) vs. 3.9/3.0 days (1.2 - 13.87) for 35 patients in the alvimopan group (p = 0.0149). The mean/median hospital cost of the placebo arm patients was $16,735/$13,731 vs. $12,965/$11,287 for the alvimopan patients (p = 0.0096). The mean/median pharmacy cost for the placebo arm patients was $1132/$614 vs. $625/$437 for the alvimopan patients (p = 0.0369). There were no significant differences in readmission rates (16.7% vs. 11.4%, p = 0.75) or return to the operating room (7.1% vs. 2.9%, p = 0.62) between the patients receiving placebo or alvimopan. Conclusions. The addition of a peripherally acting μ-opioid receptor antagonist, alvimopan, to an established fast track enhanced recovery protocol for cancer patients undergoing resection of their intestinal malignancy results in significantly decreased LOS and overall decreased treatment cost.

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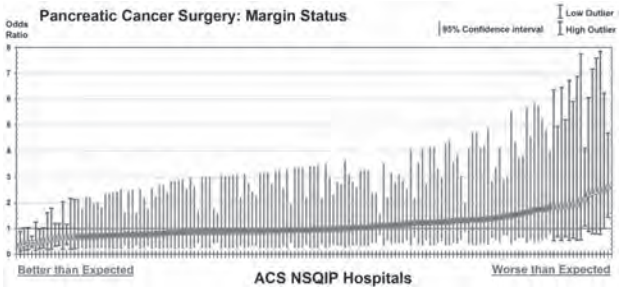
Should Margin Status Be Monitored as an Outcome Following Pancreatic Cancer Surgery? R.P. Merkow,[1]* D.J. Bentrem,[2] H.A. Pitt,[3] J.L. Paruch,[1] A. Stewart,[1] D. Winchester,[1] C.Y. Ko,[1] K.Y. Bilimoria.[1] *1. Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL; 2. Department of Surgery, Surgical Outcomes and Quality Improvement Center and the Northwestern Institute for Comparative Effectiveness Research (NICER) in Oncology, Northwestern University, Chicago, IL; 3. Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.*

INTRODUCTION: Surgical margin status is an important outcome following pancreatic cancer surgery however variation in pathologic review practices may limit its use as a quality indicator. Nevertheless, risk-adjusted hospital assessment could potentially identify lower or higher than expected margin involvement rates for internal standardization and quality improvement efforts. We sought to evaluate the feasibility and reliability of measuring hospital performance based on surgical margin involvement. METHODS: Patients from the ACS NSQIP and NCDB who underwent pancreatic resection for Stage I-III cancer were linked (2006-2009). Risk-adjusted surgical margin involvement (R1/R2) was evaluated using hierarchical regression methods, and the number of cases required to meet increasing reliability thresholds (i.e., amount of variability in an assessment that is due to a real difference in performance) was determined. RESULTS: From 153 hospitals, 2482 patients underwent pancreatic resection for cancer and 533 (21.5%) had an involved surgical margin. Factors associated with margin positivity were T-stage (T3: OR 3.21, 95% CI 1.73-5.98; T4: OR 11.00, 95% CI 5.16-23.42; vs. T1), N-stage (N1: OR 1.52, 95% CI 1.19-1.95; vs. N0), vascular reconstruction (OR 1.53, 95% CI 1.05-2.22), and tumor size (2-4.9cm: OR 1.59, 95% CI 1.01-2.50, ≥5cm: OR 1.89, 95% CI 1.14-3.14; vs. <2cm). Patient demographics and comorbidities were not associated with an increased likelihood of involved surgical margins. At the hospital-level, the mean (SD) surgical margin involvement rate was 21.5% (41.1%) and ranged from 0 to 100%. After risk-adjustment, 2 hospitals had lower than expected and 3 had higher than expected margin involvement (Figure). A moderate reliability of 0.4 was achievable after 8 cases, whereas an excellent reliability of 0.7 was achievable after 29 cases. CONCLUSION: Despite differences in pathologic evaluation practices, hospitals can be feasibly and reliably provided comparative data on surgical margin status following resection for pancreatic cancer. Pathologic standardization would further expand its use in quality improvement efforts.



Risk-adjusted margin status hospital comparisons following pancreatic cancer surgery.

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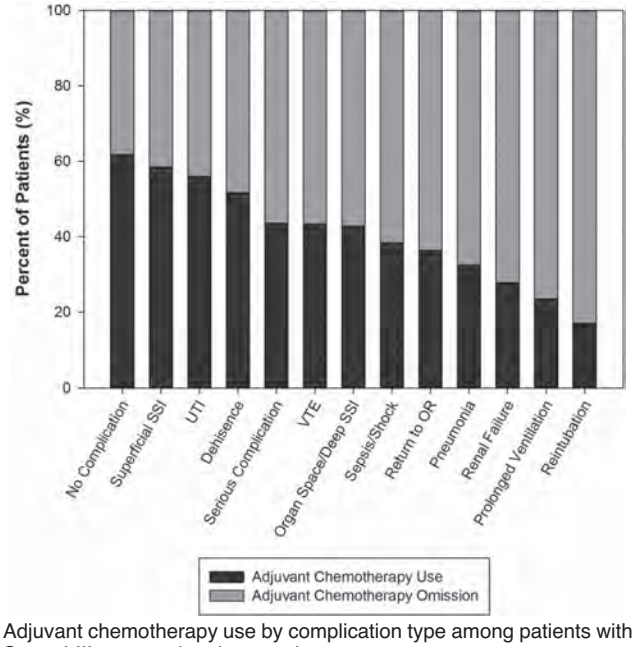
Postoperative Complications Reduce Adjuvant Chemotherapy Use in Resectable Pancreatic Cancer R.P. Merkow,[1]* K.Y. Bilimoria,[1] J.S. Tomlinson,[3] J.L. Paruch,[1] A. Stewart,[1] D. Winchester,[1] C.Y. Ko,[1] D.J. Bentrem.[2] *1. Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL; 2. Department of Surgery, Surgical Outcomes and Quality Improvement Center and the Northwestern Institute for Comparative Effectiveness Research (NICER) in Oncology, Northwestern University, Chicago, IL; 3. Department of Surgery, University of California, Los Angeles (UCLA) and VA Greater Los Angeles Healthcare System, Los Angeles, CA.*

INTRODUCTION: Randomized trials have demonstrated a survival advantage with adjuvant chemotherapy in localized pancreatic cancer. Pancreatic resection is associated with significant morbidity, however the degree to which complications limit subsequent treatment options is unknown. Our objective was to assess the impact of postoperative complications on the receipt of adjuvant chemotherapy in a multicenter evaluation. METHODS: Patients from the ACS NSQIP and NCDB who underwent pancreatic resection for cancer were linked (2006-2009). The associations between complications and adjuvant chemotherapy use or treatment delay (≥70 days from surgery) were assessed using multivariable regression methods. RESULTS: From 149 hospitals, 2249 patients underwent resection for Stage I-III pancreatic adenocarcinoma. Patients treated with neoadjuvant therapy (n=202, 9.0%) were excluded. Of the remaining 2047 patients, 23.2% had at least one serious complication. Adjuvant chemotherapy receipt was 57.7%: 61.4% among patients not experiencing any and 43.6% among those who had a serious complication. Serious complications increased the likelihood of adjuvant therapy omission over two-fold (OR 2.20, 95% CI 1.73-2.80). Specific complications associated with adjuvant chemotherapy omission were reintubation (OR 7.91, 95% CI 3.65-17.14), prolonged ventilation (OR 6.20, 95% CI 3.38-11.35), pneumonia (OR 2.88, 95% CI 1.66-5.00), sepsis/shock (OR 2.74, 95% CI 2.01-3.73), organ space/deep SSI (OR 2.17, 95% CI 1.52-3.11), VTE (OR 1.92, 95% CI 1.08-3.42) and UTI (OR 1.60, 95% CI 1.02-2.52) (Figure). Serious complications also doubled treatment delay (OR 2.08, 95% CI 1.42-3.05). Sensitivity analysis in a younger, healthier patient cohort demonstrated similar associations. CONCLUSIONS: Postoperative complications are common following pancreatic surgery and are associated with adjuvant chemotherapy omission and treatment delays. These multi-institutional data suggest a consideration for

neoadjuvant chemotherapy administration, particularly among patients at high-risk for the identified complications.



Adjuvant chemotherapy use by complication type among patients with Stage I-III pancreatic adenocarcinoma.

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Race Does Not Impact Pancreatic Cancer Treatment and Survival in an Equal Access Federal Health Care System S. Lee,[1]* R.L. Jeffrey,[2] C.D. Tzeng,[1] G.J. Chang,[1] S.P. Hetz,[2] J.B. Fleming,[1] J.E. Lee,[1] M.H. Katz.[1] *1. MD Anderson Cancer Center, Houston, TX; 2. William Beaumont Army Medical Center, El Paso, TX.*

Introduction: Disparities in the receipt of surgical resection for pancreatic adenocarcinoma (PDAC) have been observed with African Americans undergoing surgical resection less frequently and having inferior overall survival when compare to Caucasian counterparts. Beneficiaries in the Department of Defense (DoD) health care system have equal access to healthcare resources. We sought to determine whether differences in treatment and survival rates exist between African American and Caucasian patients with PDAC treated in an equal access healthcare system. Methods: Retrospective review of DoD tumor registry was performed to identify patients with PDAC diagnosed from 1993-2007. Patient, tumor, and treatment factors were analyzed to compare the presentation profile, resection and adjuvant therapy rates, and survival outcomes between African American and Caucasian patients. Results: Among 1723 patients with PDAC; 76% were Caucasians, 14% were African Americans, 10% were of other race. Cancers were loco-regional stage (AJCC stages I-III) at presentation in 36% of African Americans and 37% of Caucasians (p = 0.847). Among those with loco-regional cancers, the rates of surgical resection (50.9% vs. 49.1%, p=0.803), administration of chemotherapy (51.9% vs. 49.7%, p=0.764) and delivery of radiation therapy (47.1% vs. 40.9%, p=0.409) did not differ between the two groups. There was also no difference between the median overall survival (OS) of all African American and Caucasian patients (median OS 5.6 vs. 4.9 months, p=0.172), those with locoregional cancers (14.0 vs. 9.4 months, p=0.367), and those with locoregional cancers who underwent resection (20.8 vs. 12.6 months, p=0.499). Conclusions: In an equal access healthcare system, racial disparities in treatment and outcome among patients with pancreatic cancer were not observed. Improving access to healthcare among racial minorities in the general population may improve the oncologic outcome of patients treated for pancreatic cancer.

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High Risk Soft Tissue Sarcoma Biomarker Expression Patterns and Outcome Following Neoadjuvant Chemoradiation J.M. Kane,[1]* Q. Zhang,[2] A. Klimowicz,[4] A. Magliocco,[5] A. George,[2] J. Simko,[6] T. DeLaney,[3] W. Kraybill.[2] *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. Radiation Therapy Oncology Group, Philadelphia, PA; 3. Massachusetts General Hospital, Boston, MA; 4. Tom Baker Cancer Centre, Calgary, AB, Canada; 5. Moffitt Cancer Center, Tampa, FL; 6. University of California, San Francisco, San Francisco, CA.*

INTRODUCTION: Mortality from high risk (large, deep, high grade) soft tissue sarcomas (STS) remains high. Adjuvant chemotherapy has shown mixed results. Biomarker predictors of treatment response and outcome could improve patient selection for adjuvant therapies. METHODS: Tissue microarrays (TMA) for biomarker expression were created using pre and post treatment tumor from 2 prospective high risk STS trials (pilot study and RTOG 9514) of neoadjuvant mesna, adriamycin, ifosfamide, dacarbazine (MAID)/44 Gy radiation/adjuvant chemotherapy. Biomarkers included Ki67, ATM-ataxia telangectasia mutated, CAIX-carbonic anhydrase IX, ERCC1-excision repair cross complementation group 1, GLUT 1-Glucose transporter 1, p53, and PARP1- poly (ADP-ribose) polymerase-1. Biomarker expression was correlated with pathologic complete response (PCR), disease-free (DFS), and overall survival (OS). RESULTS: Specimens from 59 eligible patients were available. Median age 47 years. Median tumor size 10.7 cm. Common subtypes: 64% pleomorphic, 22% liposarcoma, and 19% leiomyosarcoma. At median follow-up of 7.3 years, DFS was 29% and OS was 41%. Data sets were 29 pretreatment (PRE), 51 posttreatment (POST), and 19 matched pairs (MP). In the MP set, CAIX and Glut1 expression significantly decreased following neoadjuvant therapy, but p53 N/C ratio increased (Table 1). In the PRE set, no baseline biomarker expression was associated with PCR, DFS, or OS. In the POST set, increased CAIX expression correlated with higher likelihood of a PCR (OR=0.04 (0.002, 0.98, p=0.05)) and increased p53 N/C ratio was significantly associated with a decreased DFS [HR =6.67 (95% CI: 1.87, 23.8), p=0.003]. No biomarkers were associated with OS in the POST set. CONCLUSIONS: Decreased CAIX and Glut-1 following neoadjuvant therapy suggest a reduction in tumor hypoxia. Interestingly, high CAIX expression post-treatment correlated with a PCR. Pretreatment biomarker expression could not predict DFS or OS in this uniformly treated high risk STS patient cohort. Post-treatment enrichment of p53 and the association of p53 expression with recurrence suggest that treatment selected for p53 mutation.

Changes in biomarker expression following neoadjuvant chemoradiation in 19 matched pair "high risk" soft tissue sarcomas.

Marker	Mean Pre Treatment values (log transformed)	Mean Post Treatment values (log transformed)	Non parametric test p-value
ACIS Ki67 Percentage (Average)	2.4	1.9	0.067
ATM Nuclear AQUA	9.0	8.9	0.50
ATM Tumor Mask AQUA	8.5	8.4	0.36
CAIX Cytoplasm AQUA	8.2	7.5	0.04*
CAIX Tumor Mask AQUA	8.2	7.6	0.02*
ERCC1 Nuclear AQUA	9.1	9.0	0.35
ERCC1 Tumor Mask AQUA	8.5	8.3	0.098
ERCC1 Nuclear/Cytoplasm ratio	1.2	1.4	0.300
Glut1 Cytoplasm AQUA	8.3	7.7	0.11
Glut1 Tumor Mask AQUA	8.3	7.8	0.05*
p53 (Average) Nuclear/Cytoplasm ratio	0.3	0.6	0.05*
PARP1 Nuclear AQUA	8.8	8.6	0.031*
PARP1 Tumor Mask AQUA	8.4	8.1	0.06

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Liposarcoma Xenograftability is Predictive of Patient Disease Specific Survival E. Shurell,* K.B. Smith, L.M. Tran, B. Tam, S. Dry, H. Wu, F.C. Eilber. *University of California - Los Angeles, Los Angeles, CA.*

Introduction: Liposarcoma (LPS) is the most common histologic subtype of soft tissue sarcoma. The molecular mechanisms that mediate tumor development remain poorly understood and few LPS model systems are available for investigation. We therefore developed a series of xenograft models that

accurately recapitulate human disease and evaluated the biological features of this model in the context of patient outcome. Methods: Surgically resected LPS samples from 22 patients were xenografted into immunocompromised mice between May 2008 and June 2010. Xenografted tumors maintained the histopathologic and gene expression characteristics of the primary tumors. Clinicopathologic data was examined for predictors of tumor engraftment and passageability. Results: Most patients had large (median size 23 cm, range 6-42 cm), high grade (72.7%) tumors located in the retroperitoneum (63.6%). 5 (23%) were myxoid LPS, 7 (32%) were WD LPS, and 10 (46%) were DD LPS. 7 samples produced palpable tumors, yielding a 32% engraftment rate. Of the engrafted tumors, all were high grade, 5 (71%) were DD LPS and 2 (29%) were myxoid LPS. 3 xenografts could be serially passaged *in vivo* to grow in subsequent mice; these tumors were all DD LPS: two originated from recurrent tumors, and one from a primary tumor with concurrent pulmonary metastases (Table 1). We analyzed patient disease specific survival (DSS) in the context of our xenograft model. Median follow up time for survivors was 25.5 months (range 5-34 months). Regardless of LPS subtype, grade, and prior treatment, the ability to engraft and/or be passaged correlated with a significantly worse DSS ($p<0.0001$, log-rank test). Patients whose tumors engrafted and were serially passaged died from disease within 6 months of tumor removal (n=3), in contrast to those patients whose tumors did not engraft (n=15). Conclusion: Our LPS xenograft model correlates with DSS, and xenograftability identifies a biologically aggressive phenotype beyond traditional clinicopathologic predictors of outcome. This model may augment current predictive tools for patient survival, and provides a platform to test novel targeted therapeutic agents and personalized therapy.

Table 1. Clinicopathologic data for liposarcoma xenografted tumors.

ID	Liposarcoma Histology	Grade	Origin of Sample	Site	Size (cm)	Treatment	Gender	Age	Patient Status
TUMORS THAT DID NOT ENGRAFT									
1	Myxoid	Low	Primary	Thigh	29	XRT	M	39	NED
2	Myxoid/RC	Intermediate	Primary	Thigh	16	XRT	M	28	NED
3	Myxoid/RC	High	Primary	Thigh	9	XRT	M	47	NED
4	WD	Low	Primary	RP	15		F	58	NED
5	WD	Low	Primary	RP	41	XRT	F	51	NED
6	WD	Low	Primary	RP	32	AC	M	61	AWD
7	WD	Low	Recurrent	RP	15		M	72	NED
8	WD	Low	Recurrent	RP	3	XRT	M	49	NED
9	WD	Low	Recurrent	RP	20	XRT	M	54	AWD
10	WD	Low	Recurrent	RP	22	XRT	M	43	AWD
11	DD	High	Primary	RP	31	XRT	F	57	NED
12	DD	High	Primary	RP	30		M	86	DOD
13	DD	High	Primary	Abdomen	13	XRT	M	66	AWD
14	DD	High	Recurrent	RP	20	XRT	F	60	NED
15	DD	High	Recurrent	RP	5	XRT	F	86	DOD
TUMORS THAT ENGRAFTED ONLY									
16	Myxoid/RC	High	Primary	Gluteal	16	AC, XRT	F	29	NED
17	Myxoid/RC	High	Metastatic	Abdomen	22	AC	M	66	AWD
18	DD	High	Recurrent	RP	5	AC, XRT	F	58	NED
19	DD	High	Metastatic	Flank	4	NC, XRT	F	61	DOD
TUMORS THAT ENGRAFTED AND COULD BE PASSAGED									
LPSX1	DD	High	Recurrent	Abdomen	12	NC, XRT	F	51	DOD
LPSX2	DD	High	Recurrent	Thigh	15	XRT	M	90	DOD
LPSX3	DD	High	Primary / Metastatic	RP	27	NC	M	75	DOD

Key: RC: round cell, WD: well-differentiated, DD: dedifferentiated, RP: retroperitoneal, XRT: radiation therapy, AC: adjuvant chemotherapy, NC: neoadjuvant chemotherapy, M: male, F: female, NED: no evidence of disease, AWD: alive with disease, DOD: dead of disease

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Vascular Leiomyosarcomas: Clinical Observations and Molecular Variables G.M. Boland,* E. Demicco, K. Lusby, D. Ingram, J.M. Palmer, A. Lazar, J. Cormier, K. Hunt, D. Lev, R. Pollock, K.E. Torres. *MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: In this report we evaluated the clinicopathologic features of vascular leiomyosarcomas (vLMS), a rare sarcoma with poor prognosis. METHODS: All adult patients with vLMS in our tumor registry and clinical database between 1/1/93 and 6/28/12 were identified. Clinical course, follow-up and outcomes were assessed with focus on patient tumor recurrence, and survival. Additionally, a vLMS tissue microarray (n = 50 specimens) was constructed for immunohistochemical analysis of molecular markers related to tumor growth, cell cycle, survival, angiogenesis, oncogenes and tumor suppressors. RESULTS: A total of 78 patients with vLMS were identified (IVC=56; femoral vein =13, and 9 in other locations including PA, SVC and renal vessels). 69 patients presented with localized- and nine (12%) with metastatic disease. All patients with localized disease except two underwent surgical resection (R0=46, R1=15, R2=6). Twenty patients received chemotherapy in addition to surgical resection, 11 received neo and adjuvant radiotherapy and nine received radiation, chemotherapy and surgical intervention. The median follow up period was 5 years (0.5-14 years). Forty-six (59%) patients developed local recurrence and 43 (55%) metastasized primarily to the liver and lung. Five- and ten-year disease-specific survival (DSS) rates were 56% and 22%, respectively for patients that underwent resection. Univariable analysis failed to identify any clinical parameter to correlate with DSS. All evaluated markers were expressed in the vLMS to varying levels. Most importantly, strong beta-catenin (HR=2.043, P=0.003) and IGFR1 (HR=3.015, P=0.002) expression correlated significantly with dismal patient outcome on statistical analysis. Beta-catenin was over-expressed in metastatic disease when compared to primary lesions (P=0.012); conversely, Bcl2 expression was decreased in recurrent and metastatic lesions when compared to primary lesions (P=0.002). CONCLUSION: vLMS exhibit enhanced propensity for metastatic spread. Molecular markers, such as beta-catenin and IGFR1 identified in this study, should be examined in prospective studies to determine their utility in the clinical decision-making for these patients.

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Dermatofibrosarcoma Protuberans: Analysis of Markers of Cell Proliferation, Invasiveness and Apoptosis, Study of Fusion COL-1α1/PDGF-β by FISH and Correlation with Relapse A.S. Molina,[1]* J.P. Duprat,[1] P.H. Figueiredo,[1] J.H. Fregnani,[2] E. Bertolli,[1] I.W. Cunha,[1] G.G. Debiasi.[1] *1. Cutaneous Oncology, Hospital A. C. Camargo, Sao Paulo, Sao Paulo, Brazil; 2. Hospital de Cancer de Barretos, Barretos, Sao Paulo, Brazil.*

Introduction: Dermatofibrosarcoma protuberans is a tumor of low incidence and present controversies in its management. It is not usually lethal but treatment can be mutilating to patient. Objectives: Evaluate immunohistochemical markers of invasiveness, apoptosis and cell proliferation, the presence of fusion genes COL-I α1/PDGF-β by FISH and surgical margins, correlate all with prognosis. Results: Of 61 patients, only 6 had relapses. No patient operated with a safety margin of at least 3 cm had recurrence. There was only one recurrence in patients treated with surgical margins of at least 2 cm. Among patients operated on HACC, those who received the first treatment at HACC had lower relapse rate than patients relapsed after treatment at another hospital, but there was no statistical significance. The frequency of translocations in these patients was 77.8%. Patients with the translocation had recurrence of 5.7%, while patients without the translocation had recurrence of 30%.The immunohistochemical markers did not correlate with the recurrence rate, but when considering only patients treated with lower margins than 3 cm there was relation with the expression of FASL. Conclusion: The surgical margins smaller than 2 cm are associated with higher recurrence rate. Among the immunohistochemical markers studied, the FASL correlated with recurrence rate in patients treated with lower margins than 3 cm. The presence of chromosomal translocation seems to influence prognosis.

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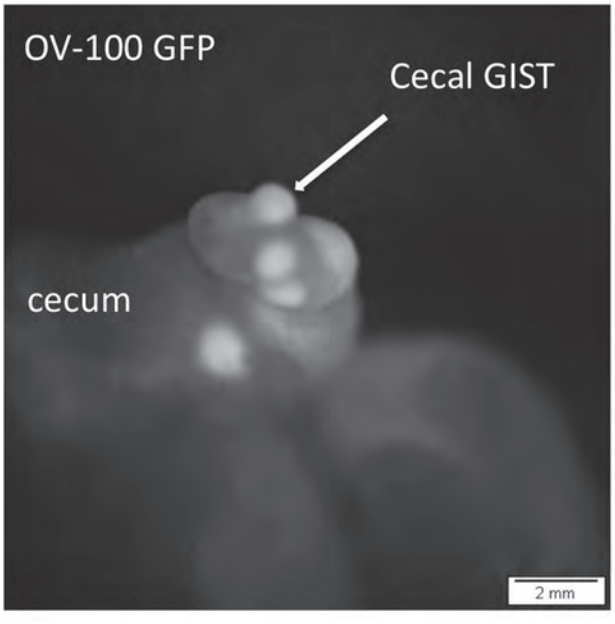
First Method for In Vivo Fluorescent Visualization of GIST C. Tang,[1] C.A. Metildi,[1]* S. Kaushal,[1] S.Y. Leonard,[1] P. Magistri,[1] S. Horgan,[1] R.M. Hoffman,[2] M. Bouvet,[1] J.K. Sicklick.[1] *1. University of California San Diego, San Diego, CA; 2. AntiCancer, Inc., San Diego, CA.*

INTRODUCTION: Gastrointestinal stromal tumor (GIST), the most common sarcoma, metastasizes hematogenously and peritoneally. Tumor-free margins and complete cytoreduction of metastatic disease are critical for decreasing recurrence. Since most GISTs overexpress KIT (c-KIT, CD117), we hypothesized that fluorescently labeled anti-KIT antibodies can improve detection of GIST. METHODS: We studied KIT K641E+/- transgenic mice that spontaneously develop cecal GIST, and wild-type C57BL/6 mice. Wistar rat anti-mouse monoclonal c-KIT antibody was labeled with the AlexaFluor 488. The conjugated anti-KIT-Alexa 488 antibody (50-100 μg) was delivered via tail vein at 24 hours prior to standard staging laparoscopy. A pediatric laparoscopic grasper was inserted in the left lower quadrant for bowel mobilization in order to visualize the cecum. All 4 quadrants of the peritoneal cavity were

examined systematically under both fluorescent and bright light. Post laparoscopy, mice were sacrificed and their abdomens exposed for Olympus OV-100 imaging. All tumors were resected and confirmed by H&E. RESULTS: We divided the mice into 4 groups. KIT K641E+/- mice received anti-KIT antibody (N=4) or isotope control (N=3). Wild-type mice received the same antibodies (N=3 per group). Fluorescence laparoscopy demonstrated the highest tumor signal-to-background noise ratio. On whole body imaging used to detect gross tumors and GFP-labeling (Fig.), there were 2 false positive and 0 false negative results, leading to an accuracy of 92%. The sensitivity, specificity, positive and negative predictive values were: 100%, 87%, 85%, and 100%, respectively. CONCLUSIONS: In this study, we present a new method for in vivo fluorescent imaging of GIST in a transgenic mouse model using labeled anti-KIT antibodies. Despite challenges from bowel auto-fluorescence, this method has several translatable applications: 1) identification of peritoneal metastases; 2) following disease response; 3) non-radioactive imaging; 4) endoscopic differentiation of gastric GISTs from leiomyomas or schwannomas; 5) laparoscopic staging; and 6) assessment of margin status. This novel approach has clear clinical applications that warrant further research and development.



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KIT Mutation Status and Multi-Visceral Resection Impact Outcomes of Neoadjuvant Therapy for Gastrointestinal Stromal Tumors B. Bednarski,* D. Araujo, M. Yi, D. Lev, A. Lazar, J. Cormier, P.W. Pisters, R. Pollock, B. Feig, K. Hunt. *Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: Management of gastrointestinal stromal tumors (GIST) has been transformed with the use of tyrosine kinase inhibitors (TKI). While data on the optimal duration of adjuvant imatinib continues to emerge, guidelines for the administration of neoadjuvant TKIs in the treatment of GIST remain unknown. Methods: Under an institutional review board-approved protocol, all patients with a diagnosis of GIST who were treated with neoadjuvant TKIs and surgical resection at our institution were identified. Clinical and pathologic characteristics were obtained from the medical record. Results: Ninety-five patients underwent surgical resection after treatment with neoadjuvant imatinib; 41 had primary GIST, while 54 patients had recurrent/metastatic disease. Median follow-up from surgery was 2.8 years. The median duration of neoadjuvant therapy was 320 (3-1611) days for primary GIST and 452 (5-2797) days for recurrent/metastatic GIST (P=0.01). While 4.9% of patients with primary GIST were treated with multiple TKIs, 40.7% of patients with recurrent/metastatic disease were exposed to >1 TKI prior to surgery (P<0.0001). Following resection of primary GIST, 82.9% of patients received adjuvant TKI therapy for an average of 673 days. Two year OS was 97.6% in patients with primary GIST and 73.7% in patients with recurrent/metastatic GIST. RFS at 2 years was 94.1% and 49.3% for primary and recurrent/metastatic disease, respectively. While no factors affected OS, the RFS for all patients was influenced by KIT mutational status (presence of exon 9, 13, or 17, HR=7.49 (95%CI 2.38-23.58)) and the need for multi-visceral resection (HR=5.20 (95%CI 1.9-14.23)). Conclusions: Neoadjuvant treatment of patients with GIST can be effectively used in the treatment of patients with both primary and recurrent/metastatic GIST. While further study is needed to delineate the optimal timing of surgery and the effects of multi-drug therapy on patient outcomes, knowledge regarding KIT mutations and the need for multi-visceral resection can serve as prognostic tools in the management of patients undergoing neoadjuvant TKI treatment.

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Neoadjuvant Chemotherapy to Define Biologic Behavior Prior to Resection of Primary Angiosarcoma J. Oxenberg, N.I. Khushalani, K.S. May, K. Attwood, J.M. Kane.* *Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: Angiosarcoma (AS) is biologically aggressive tumor with a propensity for multifocality and distant metastases. Surgical resection can be morbid, especially if AS was radiation (RT) induced. Neoadjuvant chemotherapy (NAC) may better define the biology of AS prior to considering surgery (S). Methods: Retrospective review (1996-2012) of resectable, localized AS patients (pts) treated with S or NAC followed by S (NAC-S). Patient demographics, treatment, response, and outcomes were analyzed. Results: 23 AS patients were identified. Median age was 72.9 years (17.4-88.8) and 15 were women. Primary tumor site: breast (9), head/neck (9), extremity (3), other (2). Median tumor size was 3.1cm (range 0.1-18). Cohort S had 13 pts and cohort NAC-S had 10 pts. High grade tumor: 69% S and 86% NAC-S. Previous RT: 23% S and 40% NAC-S. NAC regimens were paclitaxel (5), doxorubicin (1), gemcitabine + docetaxel (4); 20% required dose attenuation for toxicity. Following resection, complex wound closure was required in 54% S vs. 30% NAC-S. R0 resection was achieved in 85% S (although 15% required an immediate re-resection) vs. 80% NAC-S (no re-resections). The complete pathologic response rate to NAC was 30%. Postoperative wound morbidity was 62% S and 60% NAC-S. Adjuvant RT was administered in 39% S and 10% NAC-S. Adjuvant chemotherapy was given to 8% S and 10% NAC-S. At a median follow-up of 29.1 months, 2-year local recurrence (LR)-free, disease-free, and overall survival were 67.1%, 38.5%, and 61.5% for S vs. 68.6%, 54.9%, and 68.6% for NAC-S (p= 0.52, 0.66, and 0.58) respectively. Resection for a LR was performed in 38% S vs. 20% NAC-S. Additional resection for a second LR occurred in 23% S vs. 10% NAC-S. The mean number of surgical resections per patient to maintain control of the primary tumor was 1.8 for S vs. 1.3 for NAC-S. Conclusion: NAC for AS was well tolerated and did not impact perioperative morbidity. The small sample size likely limits interpretation of survival data. The number of surgical resections (and complexity of wound closure) necessary to maintain local control at the primary site seemed to favor pts who received NAC.

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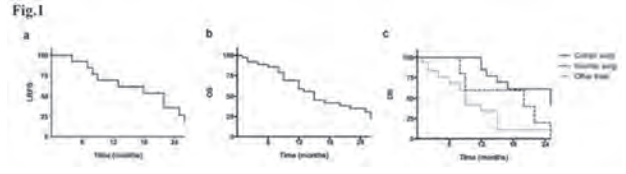
Local Recurrence after Extended Surgery for Primary Retroperitoneal Sarcoma: Is a Second Surgery Worthwhile? C. Colombo,* S. Radaelli, M. Fiore, R. Sanfilippo, S. Stacchiotti, P. Collini, C. Sangalli, C. Morosi, P. Casali, A. Gronchi. *Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.*

Objective:Some authors proposed an extended surgical approach to reduce local recurrence (LR) in patients affected by primary retroperitoneal sarcoma (RPS). Aim of the present study was to analyze the outcome of the patients who failed after such an approach. Methods:We included all consecutive patients who underwent complete resection (CR) of primary localized adult RPS at our institution. Post-relapse local recurrence free survival (LRFS) and overall survival (OS) were calculated by KM method. Results:214 pts were identified (Jan 2002-Dec 2011). At a median follow-up (FU) from first surgery of 25 mo.(IQ,11-54), 43 pts (20%) developed LR (44% female,56% male) at a median time of 12 mo.(IQ,5-23) from surgery; median age at the time of LR was 65y (IQ,56-70). The commonest histotype was DD lipo (26/69,38%), followed by WD lipo (6/48,13%), leiomyosarcoma (4/39,10%), MPNST (2/10,10%), and

SFT (1/23,4%). A total 19 of the 43 (44%) underwent a second surgical procedure: 3/6 WD lipo, 11/26 DD lipo, 2/4 leiomyosarcoma, 0/2 MPNST, 1/1 SFT. A complete macroscopic clearance of the recurrent tumor was obtained in 13 (68%): 3/3 WD lipo, 6/11 DD lipo, 1/2 leiomyosarcoma, 1/1 SFT. At a median FU of 21 mo. (IQ,9-25) from second CR, 11/13 (85%) developed a second LR. None of them underwent a 3rd surgery. LRFS at 1 and 2 yrs. were 69% and 36%(Fig.1a). Median time to second LR was 22 mo.(IQ,8-26). 5/19 pts developed distant metastases (DM) (2 pulmonary,1 extrapulmonary,2 both). Median time to DM was 23 mo. (IQ,8-28). The remaining 24 of the 43 pts were treated by CT (11), RT (1) or just observed (12). OS at 1 and 2 yrs. was 59% and 35% for the entire population(Fig.1b), 85% and 61% in the group of CR, 60% and 20% in the group of incomplete surgery and 34% and 11% in the group treated with CT/RT or just observed(Fig.1c). Conclusion:LR in RPS after a primary extended approach is challenging. Surgery can still be proposed to some pts, especially when suitable to complete resection. Nonetheless the benefit is limited- almost all pts eventually die of their disease. The combination of surgery and CT may be worth exploring, although new treatments would be definitely welcome.

Fig.1



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Prognosis of Solitary Fibrous Tumors: A Multi-Center Study
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Introduction: Solitary fibrous tumors are rare mesenchymal tumors with variable malignant potential. The majority of these tumors originate within the thoracic cavity, but they also occur in the central nervous system, head and neck, abdomen, pelvis and muscles. We report the outcome of solitary fibrous tumors treated in 9 medical centers in the Netherlands. Methods: Retrospective analysis was performed on patients with histologically-proven solitary fibrous tumors diagnosed between 1998 and 2011. Several clinical and immunohistochemical features were analysed for prognostic value. Endpoints were set at local recurrence, metastasis or death, following surgical treatment. Kaplan Meier survival curves were constructed and differences were assessed by Log-Rank tests. Results: 92 patients were identified with solitary fibrous tumors, 44 patients were female, 48 patients were male. Of these patients, 86 underwent surgical resection with curative intent, while 6 tumors were irresectable. Of all patients, 24 developed sooner or later distant metastases, while 18 patients developed local recurrence. The 5 years overall survival was 83%. The local recurrence rate was 26% at 5 years, while the metastasis rate at 5 years was 35%. Of all factors analyzed, positive surgical margins was the only factor signicantly correlating with local recurrence (p=0.01). Tumor size larger then 10cm (p=0.04), high mitotic numbers (p=0.01) and the combination of these two factors significantly correlate with higher incidence of metastases. Tumors larger then 10 cm and also a high mitotic index are also significantly correlated with lower survival. Conclusions: In this retrospective multi-center study, we show that prognosis of solitary fibrous tumors widely varies between different cases. While local recurrence is significantly higher in patients with positive margins, metastasis frequency is significantly higher in patients with large tumors and patients with a high mitotic index.

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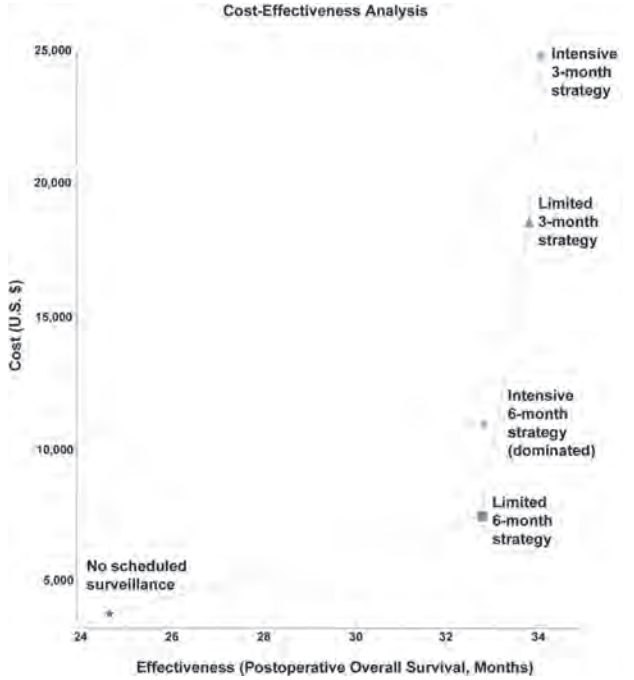
Frequency and Intensity of Postoperative Surveillance Following Curative Treatment of Pancreatic Cancer: A Cost-Effectiveness Analysis C.D. Tzeng,[1]* D. Abbott,[2] S.B. Cantor,[1] J.B. Fleming,[1] J.E. Lee,[1] P.W. Pisters,[1] G. Varadhachary,[1] S.A. Ahmad,[2] M.H. Katz.[1] *1. The University of Texas MD Anderson Cancer Center, Houston, TX; 2. University of Cincinnati, Cincinnati, OH.*

Introduction: Few data exist to guide oncologic surveillance following curative treatment of pancreatic cancer. We sought to identify a rational, cost-effective postoperative surveillance strategy. Methods: We constructed a decision-analytic (Markov) model to compare the cost-effectiveness of five postoperative surveillance strategies. No scheduled surveillance served as the baseline strategy. Clinical evaluation (comprehensive symptom assessment and physical exam) and serum carbohydrate antigen (CA) 19-9 testing without or with routine computed tomography of the abdomen/pelvis and chest x-ray at either 6- or 3-month intervals served as the four comparison strategies of increasing intensity. We populated the model with symptom, recurrence, treatment, and survival data from patients who received intensive surveillance following multimodality treatment at our institution between 1998-2008. Costs were based on Medicare payment (2011 U.S. dollars). Results: No scheduled surveillance was associated with a 24.6-month postoperative overall survival (OS) duration and a cost of $3,837 per patient. The four scheduled surveillance strategies each cost between $7,496 and $24,775 per patient and were associated with 32.8-34.1-month postoperative OS. Clinical evaluation with CA 19-9 scheduled every 6 months was associated with a 32.8-month postoperative OS and a cost of $7,496 per patient, with an incremental cost effectiveness ratio (ICER) of $5,364 per life-year (LY). The addition of routine imaging every 6 months incrementally increased cost by $3,465 without increasing OS. ICERs associated with more frequent and intensive 3-month clinical evaluations and CA 19-9 without or with routine imaging were $127,680 and $294,696 per LY, respectively. Sensitivity analyses changed the strategies' absolute costs without changing the relative ranks of their ICERs. Conclusions: In our model, increasing the frequency and intensity of postoperative surveillance of pancreatic cancer beyond a limited strategy of clinical evaluation and CA 19-9 scheduled every 6 months was associated with increased cost but no clinically significant survival benefit.



Increasing the frequency and intensity of postoperative surveillance of pancreatic cancer beyond a limited strategy of clinical evaluation and CA 19-9 scheduled every 6 months was associated with increased cost but no clinically significant survival benefit.

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Neoadjuvant FOLFIRINOX for Pancreatic Cancer: Is the Clinical Reality Worth the Hype? B.A. Boone,* J. Steve, N. Bahary, A.H. Zureikat, H.J. Zeh. *Surgery, University of Pittsburgh, Pittsburgh, PA.*

Introduction: Trials examining the use of the FOLFIRINOX regimen in metastatic pancreatic ductal adenocarcinoma demonstrate significantly higher response rates compared to gemcitabine based regimens. Improved response

rates may be particularly important for patients with locally advanced pancreatic ductal adenocarcinoma (LAPD). There is currently limited experience with this regimen in patients with LAPD to guide design of future trials. We examined the outcomes of patients with LAPD treated with FOLFIRNOX at our high volume Pancreatic Specialty Care Center in order to assess patient and provider acceptance, tolerability and response rates. Methods: Retrospective review of a prospectively maintained pancreatic cancer database was used to identify patients who were recommended to undergo neoadjuvant treatment with FOLFIRINOX. Clinical outcomes were reviewed. Results: Between 2/2011 and 9/2012 FOLFIRINOX was recommended for 25 patients with LAPD, 13 (52%) unresectable and 12 (48%) borderline resectable. Median age was 59. 21 patients (84%) were treated with a median of 5 cycles (Range:2-8). The results of treatment progression are displayed in the flowchart in Figure 1. 13 patients (52%) displayed a radiologic response. 6 of these patients (24%) received additional chemotherapy and/or radiation therapy prior to surgical exploration. 7 (64%) patients underwent pancreaticoduodenectomy, 2 (18%) underwent distal pancreatectomy and 2 (18%) underwent total pancreatectomy. Widespread peritoneal metastases were discovered at the time of surgery in 2 (8%) patients. A total of 4 patients (19%) demonstrated a major pathologic response after receiving FOLFIRINOX (2 complete pathologic responses and 2 near complete responses). Conclusions: The high rates of pathologic response observed in this small cohort suggest that FOLFIRINOX alone or as part of multimodality approach is a biologically active regimen in locally advanced pancreatic ductal adenocarcinoma. A considerable number of patients (16%) who were recommended FOLFIRINOX ultimately did not undergo treatment with the regimen. Future trials will need to account for significant toxicity and subject dropout.

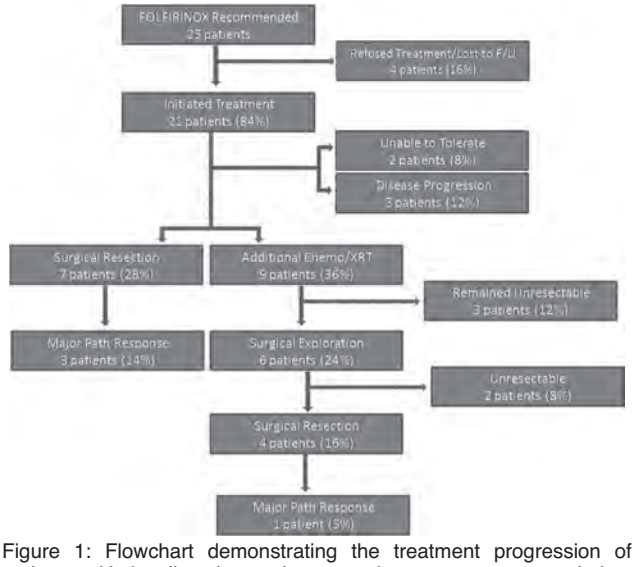

Figure 1: Flowchart demonstrating the treatment progression of patients with locally advanced pancreatic cancer recommended to undergo neoadjuvant treatment with FOLFIRINOX.

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Quality of Life in a Multi-Center Phase II Trial of Neoadjuvant Full Dose Gemcitabine, Oxaliplatin and Radiation inPatients with Resectable or Borderline Resectable Pancreatic Adenocarcinoma

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Introduction: Pancreatic cancer remains incurable for the great majority of patients afflicted with the disease. The purpose of this study was to evaluate health related quality of life (HRQoL) following neoadjuvant full dose gemcitabine, oxaliplatin and radiation therapy (30 Gy) for pancreatic adenocarcinoma in a multi-institutional Phase-II trial. Methods: Fifty-seven patients were evaluable for the HRQoL component of this trial that consisted of two cycles of neoadjuvant chemoradiation with gemcitabine and oxaliplatin followed by pancreatectomy and two additional cycles of adjuvant chemotherapy. The effects of therapy on HRQoL were evaluated using: EORTC-C30, EORTC-PAN26 and FACT-HEP. Results: There were 20 patients (35%) with untreated resectable and 37 (65%) with borderline resectable pancreatic cancer. Thirty-nine patients (69%) completed two cycles of preoperative chemotherapy and surgery, 26 (40%) underwent a pancreaticoduodenectomy and 9 (14%) a distal pancreatectomy. Twenty-six patients completed postoperative adjuvant therapy. The median age was 64 (range 42-82); patients younger than 65 had a higher global HRQoL score at 6 months (p=0.046) following the initiation of treatment. There was no difference in the HRQoL according to type of operation performed. EORTC-C30 Global HRQoL remained statistically and clinically unchanged compared to baseline levels at all time-points. FACT-Hep Trial Outcome Index and Total score showed significant statistical decline following cycle 2 of neoadjuvant treatment (p=0.002 and p=0.004), returning back to baseline levels after 6 months. This may in part be explained by a decrease in the functional (p=0.004) and physical (p=0.001) wellbeing, an increase in diarrhea (p=0.044), digestive symptoms (p=0.037) and an increased fatigue (p<0.001). Conclusion: We report that this neoadjuvant chemoradiation protocol did not have a clinical impact on global HRQoL. Overall this regimen was well tolerated with no negative effect on quality of life following the conclusion of treatment.

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Is It Time To Stop Checking Frozen Section Neck Margins During Pancreaticoduodenectomy?

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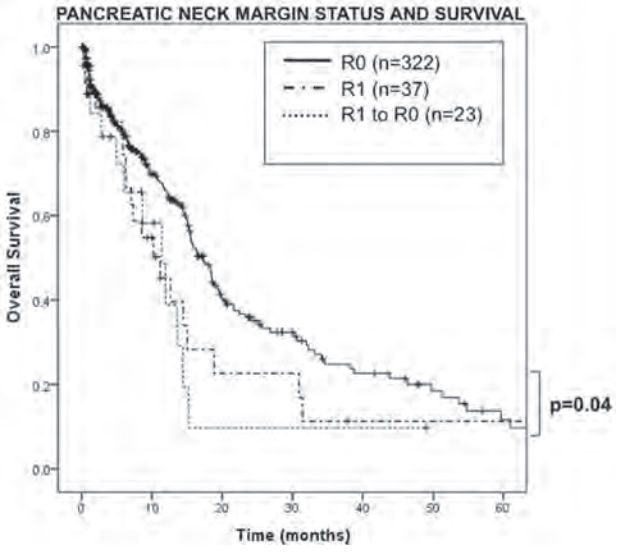
Introduction: Residual microscopic disease after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) adversely impacts survival. The value of extending the pancreatic neck resection after a positive intra-operative frozen section (FS) to achieve microscopically negative margins remains uncertain. Methods: All patients, at our institution, who had PD for PDAC from 1/2000-8/2012 were identified. Pathology reports were reviewed. Based on final permanent section analysis, patients were classified as negative (R0) or positive (R1) as determined by presence of disease at the final neck margin. The primary objective was to determine the impact of a positive FS neck margin on overall survival (OS). The secondary objective was to evaluate the value of converting an R1 margin to R0 via additional parenchymal resection. Results: 396 cases were identified. Median age was 66 years and median OS was 15.5 mos. 382 (96.4%) of 396 patients had intraoperative neck margin FS analysis, of which 53 (13.9%) were positive. On univariate analysis, positive FS was associated with larger tumor size (p=0.02), lymphovascular invasion (p=0.048), portal vein reconstruction (p=0.04), and decreased OS (11.1 months vs 17.3 months, p=0.01). Of the 53 patients with positive FS, 41 underwent additional neck resection but 18 (34%) remained R1 and 23 (43.4%) were converted to R0. On final permanent section analysis, R0 neck margin resection was achieved in 322 patients (84.3%), R1 resection in 37 patients (9.7%), and R1 converted to R0 in 23 patients (6%). The R1 converted to R0 group had an 86.9% incidence of either positive nodes and/or positive retroperitoneal margins. Both the converted R1 to R0 and the R1 groups had significantly poorer median OS than that of the R0 group (11.3 months vs. 11.1 months vs. 17.3 months respectively; p=0.04, Figure). Conclusion: A positive intra-operative frozen section margin at the pancreatic neck during pancreaticoduodenectomy for pancreatic adenocarcinoma is associated with poor survival. Extending the neck resection after a positive FS to achieve R0 margin status does not improve OS, questioning the utility of FS neck margin analysis.



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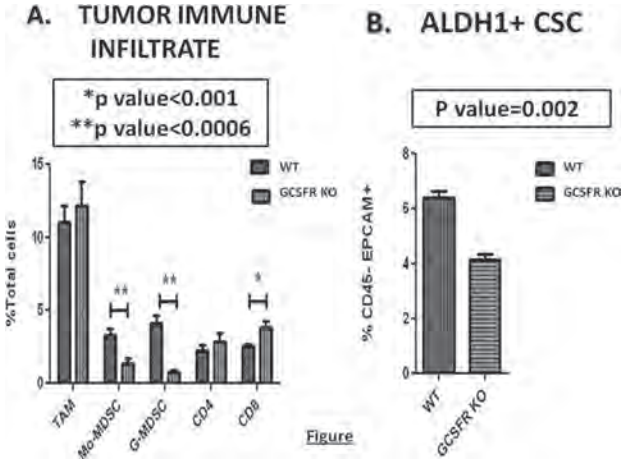
Monocytic Myeloid Derived Suppressor Cells Increase Cancer Stem Cells in Pancreatic Cancer R.Z. Panni,* D.E. Sanford, B. Belt, D.G. Denardo, P. Goedegebuure, D.C. Linehan. *Washington University in St Louis, St Louis, MO.*

Introduction: The tumor microenvironment in Pancreatic Cancer (PC) is composed of a dense myeloid infiltrate that sculpts the tumor, and may be a potential therapeutic target. MDSC are a heterogeneous group of cells with immunosuppressive properties and Granulocyte Colony Stimulating Factor (GCSF) is an important growth factor in their development. Therefore, we used a GCSF receptor knock out mouse model to study the effects of MDSC on tumor phenotype. ALDH1 is a validated marker of cancer stem cells(CSC) in PC. We hypothesize that MDSC depletion will reduce ALDH1+ CSC in pancreatic cancer. Methods: GCSFR KO mice and wild type mice were injected orthotopically with the murine PC cell line KCM. After 21 days the mice were sacrificed and flow cytometry performed on tumors for ALDH1+ CSC. RT-PCR was also conducted for the quantitative expression of transcription factors associated with stemness (such as Snail,Slug,Twist1,Nanog,Oct4 and Zeb1) on tumors. CD11b+(myeloid) cells isolated from the bone marrow of Wild type mice were co cultured with KCM for 72 hours and flow cytometry was performed to identify ALDH1+ CSC. Monocytic MDSC (Mo-MDSC) and Granulocytic MDSC(G-MDSC)were isolated by FACS from mouse tumors and were co cultured with KCM. Results: Mo-MDSC and G-MDSC were found to be significantly higher in WT as compared to GCSFR KO tumors ($p<0.0006$) where as CD8+ T cells were increased in GCSFR KO tumors ($p=0.001$).Prevalence of ALDH1+ CSC in WT tumors was significantly higher than in GCSFR KO tumors ($p=0.02$). Consistent with these findings, the quantitative expression of transcription factors associated with stemness were higher in WT tumors ($p<0.05$). ALDH1+ CSC were found to be significantly higher in KCM co-cultured with myeloid cells as compared to KCM alone. Furthermore, Mo-MDSC significantly upregulated ALDH1+ CSC when co cultured with KCM as compared to KCM alone and KCM co cultured with G-MDSC. Conclusion: Mo-MDSC increase tumor initiating cells in pancreatic cancer. Further elucidation of this phenomenon may lead to improved therapeutic targeting strategies in pancreatic cancer.



Figure

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Inhibition of Stromal TGFβR2 Inhibits Pancreatic Cancer Growth and Metastasis *In Vivo* K.T. Ostapoff,* B. Cenik, R.E. Schwarz, R.A. Brekken. *Surgery, University of Texas Southwestern, Dallas, TX.*

Introduction: TGF-β is a significant driver of pancreatic adenocarcinoma (PDAC) progression, invasion, metastasis, angiogenesis and epithelial to mesenchymal transition (EMT). However, the contribution of stromal TGF-β signaling to tumor cell phenotype and tumor progression remains unclear. Methods: Conditioned media was collected from murine 3T3 fibroblasts and murine Raw 264.7 macrophages treated with an anti-murine TGFβ receptor 2 (TGFβR2) antibody (2G8) or isotype matched control. Human PDAC cell lines Capan-1, MiaPaca-2, Colo357 and C5LM2 were treated with conditioned media from stromal cells and proliferation, migration and anchorage independent growth was investigated. The effect of 2G8 therapy was determined in SCID mice bearing orthotopic human PDAC cells. Tumor tissue was analyzed by immunohistochemistry. Results: Conditioned medium from 3T3 and Raw cells treated with 2G8 inhibited tumor cell proliferation, anchorage independent growth and migration. 2G8 induced tumor cell death and potently inhibited metastasis in 4 independent pancreatic xenografts. 2G8 therapy also decreased myofibroblast levels (α-SMA at $p<0.0001$, S100A4 at $p<0.01$) and collagen deposition in vivo. Furthermore, EMT was inhibited in 2G8 treated tumors compared to controls as measured by expression of ECAD, nuclear β-catenin and zeb1 expression. Finally, 2G8 treatment inhibited tumor associated macrophage infiltration and increased M1 macrophages while decreasing M2 macrophages thus promoting a pro-inflammatory anti-tumor immune cell phenotype. Conclusion: Inhibition of stromal TGF-β signaling inhibits primary tumor growth and metastasis. The data provide a rationale to further identify mechanisms of targeting TGF-β signaling in PDAC.

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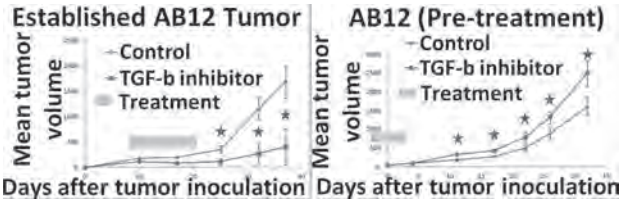
Transforming Growth Factor-β is Required for Cytotoxic T Lymphocyte-Mediated Tumor Rejection J.G. Quatromoni,[1]* E. Eruslanov,[1] O. Okusanya,[1] B.F. Judy,[1] J. Predina,[1] O. Venegas,[1] S. Albelda,[2] S. Singahl.[1] *1. Hospital of the University of Pennsylvania - Division of Thoracic Surgery, Philadelphia, PA; 2. Hospital of the University of Pennsylvania - Division of Pulmonary, Allergy & Critical Care, Philadelphia, PA.*

Introduction: Transforming growth factor (TGF)-β is a potent immunosuppressive cytokine necessary for cancer growth. To date, multiple animal and human studies have found that pharmacological inhibition of TGF-β slows and occasionally cures established tumors. We made the unexpected observation that inhibiting TGF-β before exposing animals to tumor cells paradoxically increases tumor growth kinetics. We hypothesized that TGF-β is necessary for the anti-tumor effects of cytotoxic CD8 T cells (CTLs) during the early stages of tumor initiation. Methods: Mice were pretreated with a blocking soluble TGF-β receptor (sTGF-βR) or IgG2a (control) before tumor inoculation. Tumor size was then followed for 6 weeks. In vivo lymphocyte assays and depletion experiments were performed to investigate the immunological basis of our results. Lastly, animals were pretreated with sTGF-βR or IgG2a before

immunization with an adenoviral vector encoding the human papillomavirus E7 gene (Ad.E7). Splenic E7-specific CD8+ T cells were then quantified using flow cytometry. Results: TGF-β inhibition induced by the administration of sTGF-βR before the injection of tumor cells resulted in an increased tumor growth rate ($p<0.05$) at multiple time points compared to control mice. This effect was due to inhibition of the generation of CTL, as it was abolished in SCID and CD8+ T cell-depleted mice. Pretreatment with sTGF-βR inhibited tumor-specific CTL activity in a Winn Assay, as tumor cells mixed with CD8+ T cells from tumor-bearing mice pretreated with sTGF-βR grew to a much larger size than tumors mixed with control CD8+ T cells ($p<0.05$). Furthermore, pretreatment with sTGF-βR inhibited the generation of E7-specific CD8+ T cells compared to control Ad.E7-immunized mice (0.6% total CD8+ T cells vs. 1.9%; $p<0.05$). Conclusion: These studies provide the first in vivo evidence showing that TGF-β may be necessary for the generation of anti-tumor immune responses in certain cancers. This finding has important implications for our understanding of the generation of anti-tumor immune responses, the role of TGF-β in the immune system, and in the future development of TGF-β inhibiting drugs.



sTGF-βR administered after tumor inoculation resulted in decreased tumor growth rates compared to controls (left) while sTGF-βR administered before tumor inoculation resulted in increased tumor growth rates compared to controls (right). (* indicates statistically significant difference, i.e., $p<0.05$)

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Heparanase Inhibition Reduces Vascular Function, Collagen Deposition and Potently Inhibits Tumor Growth and Metastasis in Murine Models of Pancreatic Cancer K.T. Ostapoff,* N. Awasthi, R.E. Schwarz, R.A. Brekken. *Surgery, University of Texas Southwestern, Dallas, TX.*

Introduction: Heparanase is a glycoprotein involved in extracellular matrix remodeling. Elevated heparanase expression in pancreatic ductal adenocarcinoma (PDAC) correlates with decreased overall survival and increased tumor invasiveness. PG545 is a therapeutic heparanase sulfate mimetic. Methods: WST-1 assay was used to assess cell proliferation. PDAC in vivo tumor models included intraperitoneal AsPc-1, orthotopic Pan02 and MiaPaca2, and a genetic model (p48Cre/+; KrasG12D; Ink4a/Arflox/lox). Mice were treated with saline, gemcitabine (gem) or PG545 for tissue-based or survival endpoints. Tumor analysis was performed by immunohistochemistry. Vascular perfusion studies were performed prior to experiment termination after 8 weeks of treatment. Results: In vitro PG545 inhibited tumor cell proliferation, migration and anchorage independent growth. It also inhibited the proliferation of fibroblasts but not endothelial cells in vitro. In vivo, PG545 prolonged survival in two PDAC models. In endpoint studies, PG545 inhibited primary tumor growth and metastasis compared to saline or gem. Eighty percent of PG545 treated transgenic mice had areas of normal pancreas at the time of sacrifice compared to 20% in controls. PG545 significantly decreased tumor associated collagen deposition and tumor cell proliferation but increased apoptosis. PG545 but not gem reduced vascular function as evidenced by elevated intratumoral hypoxia and reduced microvessel density ($p<0.001$), tumor perfusion (high molecular weight rhodamine-dextran $p<0.0001$) and vessel permeability (high molecular weight FITC-dextran $p<0.0001$). Unlike other anti-angiogenic agents, PG545 inhibited epithelial to mesenchymal transition (increased ECAD expression $p<0.0001$ vs control, $p<0.001$ vs gem and decreased Vimentin $p<0.0001$ vs control, $p<0.001$ vs gem). Conclusion: As a single agent, PG545 prolonged PDAC survival, reduced primary tumor growth and inhibited metastasis. Effective PG545 therapy was linked to hypoxia and reduced collagen deposition. Further exploration of heparanase inhibition and its therapeutic utility for PDAC treatment appears warranted.

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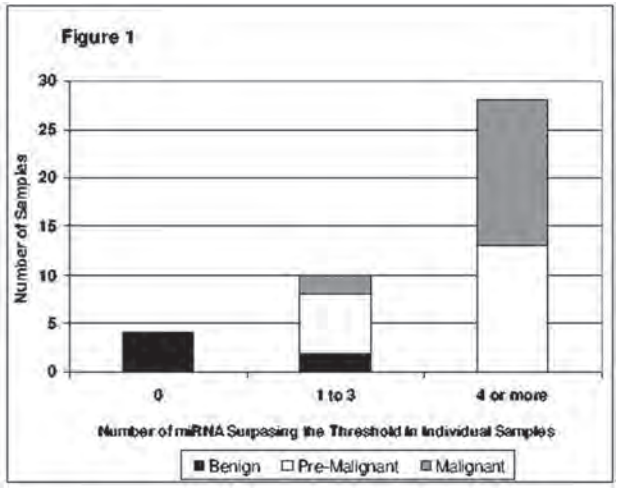
MicroRNA from Cyst Fluid Differentiates Cystic Lesions of the Pancreas J.C. Henry,[1]* J. Jiang,[2] C. Bassi,[3] G. Francesco,[2] T.D. Schmittgen,[2] M. Bloomston.[1] *1. Ohio State University Wexner Medical Center Department of Surgery, Columbus, OH; 2. Ohio State College of Pharmacy, Columbus, OH; 3. University of Verona Department of Surgery, Verona, Italy.*

Introduction: Prognostication for cystic neoplasms of the pancreas continues to evolve. Beyond simple size and CEA determination, microRNA (miRNA) promises the potential for a molecular signature for cancer risk. In this study we sought to identify miRNAs that could predict malignant potential of pancreatic cystic lesions. Methods: RNA was harvested from the cyst fluid of 72 patients with cystic neoplasms of the pancreas. Samples with adequate RNA (≥10 pg/nL) were then selected to undergo profiling by real time PCR of the 379 most common human miRNAs. All patients underwent resection and miRNA profiles were correlated with histopathology grouped by benign (serous cystadenomas), premalignant (intraductal papillary mucinous neoplasms and mucinous cystadenomas), and malignant lesions (adenocarcinoma). Results: Adequate RNA for analysis was obtained from 42 (58.3%) of the samples. Malignant lesions were more likely to have adequate RNA (N=17, 81%) than either benign (n=6, 33%) or pre-malignant lesions (n=19, 59%) ($p = 0.011$). Nine miRNA were identified as having a significant differential expression between benign and premalignant or malignant lesions. As the number of miRNA expressed by each sample increased beyond the median for the entire set the more likely the sample was to be pre-malignant or malignant (Figure 1). All premalignant or malignant lesions expressed at least one miRNA beyond the median whereas no benign lesions express less than four and only two expressed more than zero miRNA above the threshold. Conclusions: The presence of RNA in cyst fluid from patients with pancreatic cystic neoplasms may, in itself, be a predictor of premalignancy or, more likely, malignancy. miRNA can be utilized to further differentiate between purely benign, premalignant, and malignant cystic lesions of the pancreas.



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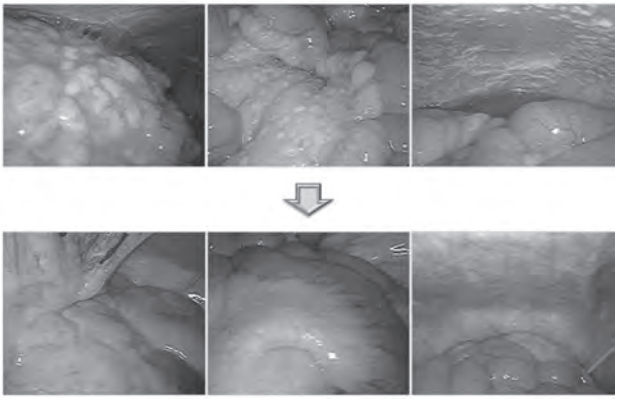
Salvage Gastrectomy after Intravenous and Intraperitoneal Paclitaxel (PTX) Combined with Oral Tegafur/Gimeracil/Oteracil Potassium (S-1) for Gastric Cancer with Peritoneal Metastasis J. Kitayama,* H. Ishigami, H. Yamaguchi, S. Emoto. *Department of Surgery, University of Tokyo, Tokyo, Japan.*

Introduction: Peritoneal metastasis is the most frequent and life-threatening types of metastasis in gastric cancer. In spite of recent advances in chemotherapeutic agents, any regimens, if administrated only via intravenous (IV) route, cannot satisfactorily control the peritoneal metastasis in gastric cancer. Although intraperitoneal (IP) chemotherapy has been proposed as a treatment option, the clinical efficacy of IP chemotherapy for peritoneal lesions has not been examined in gastrointestinal cancer. Methods: A total of 100 patients with peritoneal metastasis of gastric cancer received combination chemotherapy of S-1 plus PTX from both IV and IP routes. PTX was administered IP at

20 mg/m2 from the subcutaneous implanted peritoneal access ports as well as IV at 50 mg/m2 on days 1 and 8. S-1 was administered at 80 mg/m2/day for 14 consecutive days, followed by 7 days rest. In case of apparent downstage, gastrectomy was performed in salvage setting. Results: The median survival time (MST) of the whole 100 patients was 23.5 months. In all patients, laparoscopy was performed under general anesthesia before and after chemotherapy, and the change of peritoneal metastases was macroscopically evaluated by video-recorded picture (Figure). In 60 patients who showed apparent shrinkage of peritoneal lesions with negative peritoneal cytology after the median course of 3 (range 2-16), we performed gastrectomy with nodal dissection and R0 resection was achieved in 35 cases. The MST and 1 year overall survival of the 60 patients were 34.5 months and 83%, while those of the other 40 patients without gastrectomy were 13.0 months and 39%, respectively. Anastomotic leakage and pancreatic fistula developed in 2 cases but no mortality was observed. Conclusions: Combination chemotherapy of S-1 plus IV and IP PTX is well tolerated and very effective in gastric cancer patients with peritoneal metastasis. Systemic chemotherapy combined with repeated IP administration of PTX followed the salvage gastrectomy is a promising strategy for peritoneal carcinomatosis in gastrointestinal cancer.

Macroscopic change of peritoneal metastasis before and after combination chemotherapy with laparoscopic examination.



V1

Targeted, Surgeon-Directed, Single-Dose Intraoperative Radiation Therapy for Early Stage Breast Cancer C. Shaw,[1]* M.V. Miggins,[1] N. Bhandare,[1] J. Lightsey,[1] E.M. Copeland,[1] A. Yeung,[1] S.R. Grobmyer.[2] *1. Surgery, University of Florida, Gainesville, FL; 2. Cleveland Clinic, Cleveland, OH.*

Breast conservation therapy including partial mastectomy followed by whole breast irradiation has been widely accepted as an alternative to mastectomy for patients with early stage breast cancer. Recent evidence suggests that partial breast irradiation is a safe alternative to whole breast irradiation for many patients with early stage breast cancer. Single-dose, low kilovoltage intraoperative radiation therapy is the only type of partial breast irradiation to date which has been shown to be effective in a prospective randomized trial (International TARGIT trial). Our technique of partial mastectomy, sentinel node biopsy, and treatment with single-dose, low kilovoltage intraoperative radiation therapy for early stage invasive ductal breast cancer is demonstrated in this video. Highlighted are the considerations of performing partial mastectomy for patients having single-dose intraoperative radiation therapy, including cavity sizing and preparation, applicator placement, and closure. The excellent published oncologic results, the simplicity of the technique, and the shortened duration of treatment and recovery for patients favor the widespread adoption of this technique.

V2

Employing Unique Surgical Strategies for Advanced Adrenocortical Carcinoma: A Chance to Achieve Disease Control and Survival N.N. Nissen,* T.B. Tran, V.G. Menon. *Cedars-Sinai Medical Center, Los Angeles, CA.*

Purpose: Adrenocortical carcinoma (ACC) is a rare malignancy frequently diagnosed in advanced stages and oftentimes extends to nearby visceral and vascular structures. Surgery remains the most effective long-term solution for ACC. Patient and Methods: We describe in this video a case of a 45-year old healthy female who underwent surgery for hypercortisolism secondary to a functional adrenal tumor invading the inferior vena cava (IVC). We utilized intraoperative ultrasound to demonstrate a tumor thrombus with nearly complete obstruction the vena cava. Venovenous bypass was performed to allow for complete en bloc resection of the adrenal mass with portion of the vena cava, which was repaired using synthetic vein graft. Though pathology confirmed high grade ACC with clear margins, 7 months later, the patient had recurrence and successfully underwent resection of the caudate lobe of the liver. The patient experienced no postoperative complications. Currently, the patient has no evidence of recurrence and continues to demonstrate adequate disease control. Conclusions: This report demonstrates that complete resection of a complex adrenal malignancy invading the inferior vena cava is feasible and can be safely performed by utilizing venovenous bypass in selected patients. Oncologic principles can be achieved by performing IVC resection and reconstruction in combination with en bloc tumor removal. Given the lack of effective chemotherapy, en bloc resection of the tumor as well as resection of any metastases can potentially improve survival outcomes for patients with ACC.

V3

Peritonectomy Procedures for the Treatment of Peritoneal Metastases L. Bijelic,* J. Hong, P.H. Sugarbaker. *Surgery, Washington Hospital Center, Washington, DC.*

Peritonectomy procedures form the basis for effective surgical cytoreduction of peritoneal metastases. This surgical technique has led to the development of cytoreductive surgery combined with heated intraoperative intraperitoneal chemotherapy (HIPEC) as a treatment option for patients with peritoneal metastases from appendiceal, colorectal, ovarian and other cancers. This video shows the surgical treatment of extensive peritoneal metastases in a 52 year old female with mucinous appendiceal malignancy using cytoreductive surgery and HIPEC. All peritonectomy procedures that constitute the cytoreductive surgery approach are represented along with the use of HIPEC. At the time of exploration, the patient was found to have mucinous tumor deposits involving the undersurface of both the right and left hemidiaphragms, the greater omentum, the anterior parietal peritoneum including the paracolic sulci and the pelvic peritoneum. The surgical techniques necessary to remove all of the deposits are depicted including stripping of the diaphragms, greater omentectomy with splenectomy, anterior parietal peritonectomy and pelvic peritonectomy with en bloc hysterectomy and bilateral oophorectomy.Following complete removal of tumor, hyperthermic intraperitoneal chemotherapy is administered. The administration of HIPEC using the open method is described and briefly depicted. We conclude that peritonectomy procedures can be used effectively to achieve complete surgical cytoreduction of extensive peritoneal metastases. Complete cytoreduction is one of the most important prognostic factors in patients undergoing surgery for treatment of metastatic disease.

V4

Thoracoscopic Access Facilitates Safe Exposure of Posterior/Superior Liver Lesions in Patients Ineligible for Laparoscopy C. Conrad,[1]* M. Nedelcu,[2] A. Camerlo,[2] N. Simvathirtan,[2] K.K. Tanabe,[3] B. Gayet.[2] *1. Dana-Farber/Partners CancerCare Surgical Oncology Fellowship Program, Boston, MA; 2. Institute Mutualiste Montsouris, Paris, France; 3. Massachusetts General Hospital, Boston, MA.*

INTRODUCTION: Laparoscopic Resection of lesions in Couinaud's segment VIa are considered difficult due to superior/central location; especially in patients with prior abdominal operations. In the video we present the benefits and challenges of a thoracoscopic approach to a lesion in SIVa. HISTORY: A 67 year old male suffered from sigmoid colon adenocarcinoma (pT3, N2 (6/26), M1 (liver SII and SIII) three years prior. He had undergone a laparoscopic sigmoid coloectomy, metastasectomy and Folfox 4. One year later he presented with three recurrent liver metastasis located between SVII/SVIII, SVI and SIV, treated with laparoscopic right hepatectomy and wedge resection of SIV. Complications were bile leak and abscess requiring drainage. He now presented with a recurrence in SIVa . Due to his multiple prior abdominal operations and infections the patient underwent a transthoracic approach. OPERATION: After single lumen intubation, the patient was positioned in a modified French position (30° tilted to left, legs split apart, knees flexed, right arm positioned above the head). Three 5 mm trocars are placed midaxillary,

intercostal 7 and midclavicular in interspaces 7 and 9. A 10mm trocar is placed midaxillary in interspace 9. CO2 insufflation is used to displace the lung at 12 mmHg. A pleurolysis is necessary to expose the diaphragm. Transdiaphragmatic ultrasound is used to identify the lesion. An axial phrenotomy is performed, which is resected non-anatomically with a 1cm margin. The specimen is extracted, a drain placed and the diaphragm closed with a running suture. The patient recovered without any complication. CONCLUSION: This video demonstrates the feasibility of a transthoracic liver resection for patients with a non-virgin abdomen. This approach allows for a safe laparoscopic approach and facilitates exposure of lesions in posterior/superior location. However, inflow control using a Pringle maneuver and bleeding from hepatic veins could be difficult to control and the surgeon must be prepared for staged conversion as well as familiar with a posterolateral approach to the hepatoduodenal ligament for inflow control.

V5

Laparoscopic Placement of Biologic Spacers to Facilitate Dose Intense Radiotherapy for Unresectable Hepatic Malignancy
T.A. Aloia,[1]* A.B. Haynes,[1] J. Vauthey,[1] C. Ferrone,[2] C. Crane,[1] S. Krishnan,[1] J.Y. Wo,[2] T.S. Hong,[2] S.S. Yoon.[2] *1. Surgical Oncology, UT-MD Anderson Cancer Center, Houston, TX; 2. Massachusetts General Hospital, Boston, MA.*

Introduction: Delivery of radiation therapy (RT) to treat unresectable liver tumors is frequently limited by close proximity of radiation-sensitive organs. Methods: This video documents the placement of a biologic mesh spacer (BMS) composed of acellular human dermis using a laparoscopic technique to facilitate delivery of dose-intense radiotherapy to a 20 cm intrahepatic cholangiocarcinoma. The patient (pt) is a 63 year old woman whose only prereferral treatment was transarterial chemoembolization x 2, with minimal response. Initially, she was not considered a candidate for radiotherapy due to proximity of bowel to tumor. Included in the video are preoperative CT images as well as the isodose curves used for radiation treatment planning. These images demonstrate the safety margin to the stomach that was achieved with the BMS. On postoperative day 26, the pt initiated intensity modulated radiation therapy with 6 MV photons dosed to 96% to a total dose of 58.1 Gy over 15 fractions at 3.7 Gy per fraction. She completed all intended doses and experienced no bowel toxicity. 3-months post treatment scans demonstrated near complete necrosis of the tumor. Results: This novel technique has been performed under IRB approved protocols on 14 pts with unresectable liver tumors who were previously unable to receive RT due to risk of bowel toxicity. Median length of stay was 2.5 days (range 1-8 days), with 3 pts developing low-grade complications (abdominal wall hematoma, cellulitis, ileus). Postoperative imaging confirmed eligibility to receive RT with 2-5cm buffers to sensitive structures. Two pts did not receive RT due to extrahepatic disease progression. For the remaining 12 pts, RT was delivered by PBRT in 8 pts, IMRT in 3 pts, and SBRT in 1 pt. Median total RT dose delivered was 54 Gy (range 40-58.5 Gy) in 5-15 fractions, with no reports of grade 3-4 bowel toxicity. At last follow-up, local disease control was obtained in 11 of 12. None of the BMS required removal. Conclusions: Initial dual institution experience with this novel technique demonstrates safety and efficacy, allowing previously untreatable liver tumor patients to receive high-dose RT.

V6

Single Incision Intragastric Surgery for T1a Gastric Cancer C. Conrad,[1]* M. Nedelcu,[2] A. Camerlo,[2] N. Simvathirtan,[2] K.K. Tanabe,[3] B. Gayet.[2] *1. Dana-Farber/Partners CancerCare Surgical Oncology Program, Boston, MA; 2. Institute Mutualiste Montsouris, Paris, France; 3. Massachusetts General Hospital, Boston, MA.*

INTRODUCTION: T1a Gastric cancer not amendable to endoscopic mucosal resection (EMR) is often located close to the esophagogastric junction and despite the early stage of cancer requires an esophago-gastrectomy. Based on our prior multiport intragastric laparoscopic experience, we performed the first reported single incision laparoscopic intraluminal resection (SILS) in humans. HISTORY: The patient is a 72 year old male with reflux symptoms. Endoscopy demonstrates a 1x1cm erythematous area below the esophagogastric junction. Biopsies confirmed a superficial gastric adenocarcinoma in a zone of high grade dysplasia. Endosonography is consistent with a T1a gastric cancer and CT scans of chest and abdomen are negative. An EMR led to only incomplete removal of the cancer with positive lateral margins and therefore a SILS intragastric resection is planned. OPERATION: The patient is positioned in the French position (supine, legs split apart, knees flexed). The abdomen is entered via a 3cm midline incision in the epigastrium and the stomach approximated to the abdominal wall with stay sutures. After gastrotomy, a SILS Port is placed into the stomach. The stomach is insufflated to 12 mmHg and the lesion identified. To facilitate visualization of the boarders indigo carmine is sprayed onto the lesion. Using an ultrasonic cutting device and a bipolar forceps the lesion is removed monoblock at the submucosal level. The mucosa is approximated using an automated articulating needle driver and PDS sutures. Pathology confirms a T1 gastric adenocarcinoma with negative margins. CONCLUSIONS: This video demonstrates the feasibility and safety of a SILS intragastric resection. This patient was not amendable to EMR and would have required an extensive resection including potentially a thoracotomy. SILS intragastric resection is an excellent option for patients not candidates for EMR or have comorbities that prevent extensive resection. Further, intragastric surgery allows for the immediate identification and management of perforation. SILS intragastric resection is an effective alternative to EMR for patients with T1a gastric cancer, symptomatic benign lesions or presumed benign lesions with suspicion for malignancy.

V7

Video: A Technique for Laparoendoscopic Resection of Posterior Fundic Gastric GISTs without Need for a Gastrotomy A.V. Maker,[1]* D. Patel.[2] *1. Department of Surgery, Division of Surgical Oncology, University of Illlinois at Chicago, Chicago, IL; 2. Creticos Cancer Center at AIMMC, Chicago, IL.*

Introduction: The majority of GI stromal tumors (GISTs) are located in the stomach. With increased experience in minimally invasive oncologic surgery, gastric GISTs are being increasingly approached laparoscopically. Posterior proximally located gastric GISTs can be challenging to approach laparoscopically and excise with an adequate margin without an anterior or posterior gastrotomy. **Methods:** The left sided gastrocolic and gastrosplenic ligaments are divided below the gastroepiploic vessels to allow mobility and access to the proximal posterior stomach. The left lateral segment of the liver is mobilized to allow anterior reflection of the gastric fundus and exposure of the posterior wall. Intraoperative ultrasound confirms the location and extent of the tumor base. Upper endoscopy is performed to confirm tumor location and insure no multifocality. Traction sutures are placed around the tumor to distract it from the anterior gastric wall, rotate the posterior wall laterally, and expose the base of the tumor. The number and location of the sutures is determined by the size of the tumor. With antero-lateral rotation of the stomach using the stay sutures, an endoGIA stapler approximates the posterior fundic wall under the base of the lesion insuring an adequate margin and eliminating gastric spillage. Appropriate stapler placement and margins are assisted real-time endoscopically. The stapleline is tested for leaks and inspected for hemostasis laparoendoscopically. **Results:** Complete resection of GISTs with adequate margins is performed with sound oncologic principles and demonstrated in tumors of varying sizes and locations in the proximal posterior stomach. **Conclusion:** This video demonstrates a simple laparoendoscopic technique to quickly localize even small tumors, visually confirm adequate margins, and excise gastric GISTs without spillage or gastrotomy that are located in a typically difficult area of the stomach to approach laparoscopically.

ABSTRACTS

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P1

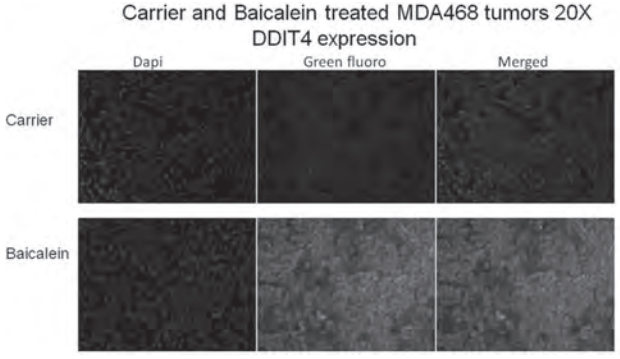
Early Results of Therapeutic and Prophylactic Nipple-sparing Mastectomy with Immediate Reconstruction in BRCA Mutation Carriers L. Lei,* K.J. Kansal, R. Tang, A.S. Colwell, S. Coopey, M.C. Specht, M.A. Gadd, W.G. Austen, B.L. Smith. *MGH, Boston, MA.*

Background: BRCA gene mutations confer a 60-80% lifetime risk of breast cancer, and carriers often consider prophylactic mastectomies to reduce risk. Nipple sparing mastectomy (NSM) provides a superior cosmetic outcome, making risk-reducing surgery more acceptable, but concerns have been raised about the oncologic safety of nipple sparing in BRCA mutation carriers. We examined the safety and early outcomes of NSM in BRCA mutation carriers. Methods: Retrospective review of NSM in our institution from 6/2006-9/2012 was performed and patients with BRCA mutations identified. Nipple sparing techniques included excision and histological analysis of ductal tissue from within the nipple. Patient and tumor characteristics, complications and early recurrence data were collected. Results: 70 BRCA mutation carriers (41 BRCA1, 29 BRCA2) underwent bilateral NSM removing 140 breasts in total. 27 NSM were for known cancers (19%) and 113 were prophylactic (81%). Median patient age was 41 (range 23-64). Reconstructions included 72 single stage implants, 60 tissue expanders and 8 other types. 2 of 113 prophylactic NSM (2%) had unexpected malignancy: 1 invasive ductal cancer and 1 DCIS; neither had tumor in excised nipple duct tissue. Mean tumor size in therapeutic NSM was 1.6 cm (range 0.2-2.9 cm) and mean tumor to nipple-areola complex (NAC) distance on imaging was 4.4 cm (range 3-10 cm, 5 unknown). 1 of 27 therapeutic mastectomies (4%) showed DCIS in the excised nipple duct tissue and the NAC was removed. At 11 months median follow-up (range 0-40 months) no therapeutic or prophylactic BRCA mutation carrier had a NAC recurrence. 2 of 27 cancer patients had a local recurrence outside the nipple: 1 chest wall/axilla and 1 axilla alone. Postoperative complications were infrequent: 2/140 (1%) nipple necrosis, 2/140 (1%) skin necrosis, 5/140 (4%) loss of implant due to infection, and 4/140 (3%) hematoma. Conclusions: Nipple duct involvement by tumor is uncommon in BRCA mutation carriers undergoing prophylactic and therapeutic nipple sparing mastectomies. Nipple sparing mastectomy is an option for BRCA carriers.

P2

Baicalein Induces Tumor Suppression in Triple Negative Breast Cancer while Increasing DDIT4 Expression in an Orthotopic Breast Cancer *In Vivo* Model A.K. Arrington,* Y. Wang, J. Yan, Q. Xing, J. Yim. *City of Hope, Duarte, CA.*

Background: Baicalein, the active component of the natural herb Scutellaria baicalensis (SB), may have a role in breast cancer treatment. We have previously shown that baicalein enhances breast cancer tumor arrest by suppressing the mTOR/S6K1 pathway via DDIT4 in vitro. We hypothesize that intraperitoneal baicalein in an orthotopic breast cancer mouse model of human triple negative breast cancer will increase DDIT4 expression and decrease tumor growth. Methods: Human triple negative breast cancer MDA468 cells were implanted orthotopically in the mammary line of SCID-bg mice. Tumors were allowed to grow for 1 week. Animals were then treated with either 20 mg/kg/day of intraperitoneal baicalein 5 days/week, a one-time dose of intraperitoneal cisplatin at 6mg/kg, or carrier control, and followed for 3 weeks for growth. Animals were sacrificed and tumor volumes were measured. For immunofluorohistochemistry (IFHC), animals were sacrificed after one week of treatment, 4 hours after the last dose of baicalein. Tumors were frozen in liquid nitrogen and underwent IFHC using DDIT4 antibody and FITC labeled anti-IgG secondary antibody. Images are from representative tumors of 3 mice per treatment. Results: Treatment of animals with baicalein yielded tumor suppression of 51.2% ($p<0.01$) when compared to control at 21 days. This is similar to the tumor suppression seen with cisplatin (60.9%, $p<0.01$). Both treatment groups had decreased tumor growth of 25% by day 12 when compared to control ($p<0.01$). Baicalein injected mice showed no evidence of toxicity with no weight loss or deaths, while one cisplatin treated mouse died. Baicalein increases DDIT4 expression by IFHC when compared to untreated tumors. Conclusions: Baicalein markedly increases DDIT4 expression in an orthotopic breast cancer mouse model. Baicalein decreases tumor growth at a similar rate as cisplatin, with no evidence of toxicity. These findings suggest a role for baicalein as a natural adjunct for treatment of breast cancer.



P3

Decision Making in Breast Cancer Surgery: Where do Patients go for Information? H. Schmidt, A. Cohen, J. Mandeli, C. Weltz, E.R. Port.* *Surgery, Dubin Breast Center/ Mount Sinai Medical Center, New York, NY.*

Patient decision-making regarding breast cancer surgery is multi-factorial, and patients derive information on surgical treatment options from a variety of sources which may have an impact on choice of surgery. We investigated the role of different information sources in patient decision making regarding surgery for breast cancer. Methods: 268 patients with newly diagnosed breast cancer (DCIS or invasive) who had surgery at our institution and were eligible for breast conserving therapy (BCT) were surveyed in the immediate preoperative period. This survey was designed to evaluate the scope and features of patient-driven research regarding their ultimate choice of surgical treatment. Pertinent clinical data for surgical decision making including family history, genetic testing, and use of MRI prior to surgery were also collected. Results: Mean patient age at diagnosis was 56 (range: 28-87). The most common source of information reported by 199/268 (74%) patients was written material received from treating breast surgeons (See Table). Internet sources were utilized by 184/268 (69%) patients. Univariate analysis did not identify any research source to be significantly related to type of surgery chosen. There was a trend for women who chose bilateral mastectomy to use the internet more frequently than those choosing unilateral mastectomy ($p=0.056$). Number of surgeons consulted, genetic testing, and MRI were significant predictors of patient choice of having mastectomy over BCT. Multivariate analysis showed that number of surgeons consulted ($p < 0.001$) and genetic testing ($p < 0.001$) were independent predictors of patient choice of mastectomy, whereas having an MRI was not. 107/268 (40%) patients reported their research was influential in their choice of surgery. Conclusions: This study evaluated the extent and nature of patient-driven research and its role in decision making for breast cancer surgery. Patients cited utilization of material provided by their surgeon and the internet as the most frequent sources of information. Understanding the factors driving patient decision making may promote more effective education for patients requiring surgery for breast cancer.

Type of Information Source

Written material from surgeon	199/268 (74%)
Total Internet use	184/268 (69%)
National Cancer organizations	145/184 (79%)
Foundations	116/184 (63%)
Institutional	121/184(66%)
Chat rooms	17/184(9%)
Blogs	32/184(17%)
Lay press	95/268(35%)
Medical Journals	81/268(30%)
Written materials from family or friends	79/268(29%)
Books	78/268(29%)

P4

Ductal Carcinoma *In Situ* and Invasive Breast Cancer Phenotype is Highly Concordant in BRCA Mutation Carriers: Implications for Prevention R.L. Yang,* R.R. Kelz, H.L. Graves, K.L. Nathanson, S.M. Domchek, P.J. Zhang, B.J. Czerniecki. *University of Pennsylvania Health System, Philadelphia, PA.*

Background: Prior studies report conflicting evidence about the existence of a ductal carcinoma in situ (DCIS)-associated premalignant pathway in patients with BRCA1/2 mutations. We report the prevalence of DCIS in mutation carriers with invasive ductal carcinoma (IDC) and compare the characteristics of DCIS to IDC. Methods: We identified BRCA1/2 mutation carriers who had surgery for IDC at a large academic hospital (1993-2010). Pathology specimens were examined for DCIS and stained for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu. Rates of IDC with DCIS (IDC+DCIS) were examined by mutation status using the Chi Square test. In IDC+DCIS, Pearson correlation coefficients were calculated to compare the percentages of ER positive nuclei (ER-PN), PR positive nuclei (PR-PN), staining intensity of HER2/neu, and nuclear grade in the DCIS and the IDC. Results: We identified 89 IDCs, of which 62.9% were BRCA1-associated and 37.1% were BRCA2-associated. 71 (80%) of IDCs had DCIS. Of BRCA1-associated IDCs, 45 (80.4%) had DCIS, and of BRCA2-associated IDCs, 26 (78.8%) had DCIS (p=0.85). BRCA1-associated DCIS was ER positive in 16%, PR positive in 20%, and HER2/neu 3+ intensity in 0% of samples, while BRCA2-associated DCIS was ER positive in 80.0%, PR positive in 76.2%, and HER2/neu 3+ intensity in 7.8% of samples. In IDC+DCIS tumors, the correlation between percentage of ER-PN in the DCIS and in the IDC was 0.95 ($p<0.001$) and between percentage of PR-PN in the DCIS and in the IDC was 0.78 ($p<0.001$). The correlation between staining intensity of HER2/neu in the DCIS and in the IDC was 0.77 ($p<0.001$) and between triple negativity in the DCIS and in the IDC was 0.90 ($p<0.001$). The correlation between nuclear grade of the DCIS and of the IDC was 0.78 ($p<0.001$). Conclusions: The majority of BRCA-associated tumors had DCIS present. There was a strong correlation between tumor characteristics of the IDC and the DCIS. This argues for the existence of a DCIS-associated premalignant pathway in BRCA mutation carriers. Future efforts should aim at implementing DCIS prevention strategies in BRCA mutation carriers.

P5

Impact of Prior Radiation Therapy on Post-operative Complications in Nipple Sparing Mastectomy and Immediate Reconstruction: A Case-Matched, Risk-Adjusted Cohort Study R. Tang, K.J. Kansal,* L. Lei, S. Coopey, A.S. Colwell, M.A. Gadd, M.C. Specht, A. Taghian, W.G. Austen, Jr., B.L. Smith. *Massachusetts General Hospital, Boston, MA.*

Introduction: Prior radiation therapy is considered a relative contraindication to nipple sparing mastectomy and immediate reconstruction (NSM) due to concerns about increased risk of post operative complications. We examined the attributable risk of prior radiation on post operative complications in patients undergoing NSM in a case-matched series. Methods: We retrospectively reviewed NSM from 6/06-7/12 at our institution and matched (1:1 or 1:2) previously irradiated to unirradiated breasts. Breasts were matched for risk factors for post-operative complications including: age, smoking status, incision (periareolar vs. non-periareolar), breast volume and type of reconstruction. No patient had insulin dependent diabetes. Patient demographics, operative details and clinical outcomes were collected. Results: From 511 consecutive NSM, we matched 38 irradiated breasts with 72 unirradiated breasts. Median follow-up was 8.5 months. Among 38 irradiated breasts, 8 breasts (21%) had some complication: 6 (16%) had skin/nipple necrosis requiring additional surgical revision and 1 (3%) had an infection requiring implant removal. Overall, 3 nipples (8%) and 1 implant (3%) were lost to complications in the irradiated cohort. Among 72 matched unirradiated breasts, 9 (13%) had some complication: 3 (4%) had skin/nipple necrosis and 3 (4%) had an infection requiring implant/expander removal. Overall, 2 nipples (3%) and 3 implants (4%) were lost to complications in the unirradiated cohort. Prior radiation was associated with increased skin/nipple necrosis even when adjusted for other risk factors (Odds ratio 4.3, 95% CI 1.1-16.7; p = 0.04). There were no statistically significant differences in infection, implant loss or hematomas between radiated and unirradiated cohorts (Table). Conclusion: Although rates of skin necrosis requiring surgical revision are higher in previously irradiated breasts, implant loss is rare and nipple loss and infection are infrequent. Previous breast irradiation is not a contraindication to nipple sparing mastectomy and immediate reconstruction.

Patient characteristics and complications after NSM and reconstruction (per breast)

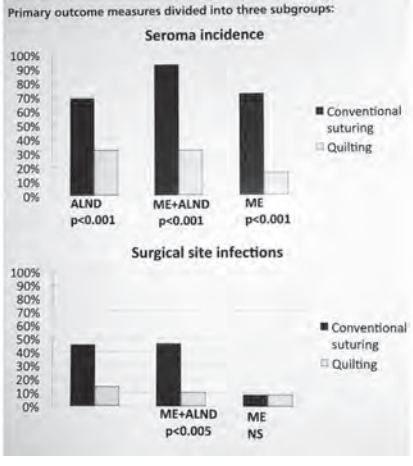
		Irradiated N=38	Unirradiated N=72	p-value
Patient characteristics				
Mean age (years)		50	49	0.5
Mean breast volume (cc)*		420	423	0.96
Mean BMI		23	24	0.5
Alloderm use		28 (74%)	51 (71%)	0.82
Therapeutic (cancer as indication for mastectomy)		22 (58%)	39 (54%)	0.84
Reconstruction	Tissue Expander	8 (21%)	16 (22%)	1.0
	Single Stage Implant	28 (74%)	53 (74%)	1.0
	TRAM	2 (5%)	3 (4%)	1.0
Complications				
Skin/nipple necrosis requiring surgical management		6 (16%)	3 (4%)	0.04
Nipple loss due to necrosis		3 (8%)	2 (3%)	0.22
Infection		1 (3%)	3 (4%)	0.57
Implant loss**		1 (3%)	3 (4%)	0.57
Capsular contracture requiring implant exchange		0 (0%)	2 (3%)	0.43
Hematoma		1 (3%)	3 (4%)	0.57

* Breast volume was calculated with a half elipsoid volume (cc) calculator using the three dimentions from the pathology gross measurement.
**All implant/tissue expander loss was due to infection.

P6

Quilting Prevents Seroma Following Breast Cancer Surgery L.J. Strobbe,* B. Ten Wolde, F. Van den Wildenberg, M. Keemers, F. Polat. *surgical oncology, CWZ, Nijmegen, Netherlands.*

Background: Seroma after mastectomy (ME) and axillary lymph node dissection (ALND) is associated with pain, discomfort, impaired mobilisation and repeated aspirations, often resulting in a surgical site infection (SSI). Minimizing dead space through fixation of the skin flaps to the underlying muscles (quilting) is hypothesized to lower the seroma incidence. The aim of this study is to evaluate the effect of quilting on seroma incidence and SSI Methods: Two consecutive groups with a total of 176 patients following ME and/or ALND were retrospectively compared. Endpoints were seroma incidence, number and volume of aspirations and prescribed antibiotics. Analysed risk factors for seroma development were age, mastectomy, lymph node dissection, neo-adjuvant therapy, body mass index (BMI) and hypertension. Results: There were no significant differences between the quilted and the traditionally closed groups regarding age, mastectomy, neo-adjuvant therapy, body mass index (BMI) and hypertension. There were significantly less node dissections in the quilted group. For this reason the results are considered for each surgical procedure separately. The quilted group (n=89) scored significant better on all endpoints compared to the conventional group (n=87) (fig1). Seroma incidence decreased from 80.5% to 22.5% ($p<0.01$), the mean number of aspirations from 3.91 to 0.55 ($p<0.01$), the volume of aspirations from 1336ml to 138ml ($p<0.01$) and the antibiotics prescribed from 31.0% to 11.2% ($p<0.01$). These results are similar for mastecomy with or without ALND. Increasing age and lymph node dissection were found to be associated with seroma, quilting was a protective factor In conclusion we found quilting to be an effective method for preventing seroma and its complications.



P7

Skin Involvement and Breast Cancer: Are All T4b Lesions Created Equal? D.L. Silverman,[1]* K. Ruth,[2] E.R. Sigurdson,[1] B. Egleston,[2] M. Boraas,[1] R.J. Bleicher.[1] *1. Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. Biostatistics, Fox Chase Cancer Center, Philadelphia, PA.*

INTRODUCTION: Nonmetastatic non-inflammatory invasive breast cancers having significant skin involvement (SI) are staged as T4b (i.e. predominantly Stage III-B), regardless of size. The prognosis of smaller skin-involved lesions remains uncertain due to their infrequency. Using a large national database, we evaluated disease specific survival (DSS) to assess whether all SI lesions should be grouped into one advanced stage. METHODS: Medicare claims linked to SEER (1992-2005) were reviewed for patients having non-metastatic invasive breast cancer with SI. Patients having inflammatory cancer, and chest wall or extra-axillary nodal involvement were excluded. SI tumors were reclassified via AJCC 7th Ed. classifications using tumor size and nodal involvement but not using SI ("New Stage"). Patients having nonSI tumors (n=66,185, extension confined to breast tissue and fat) were also restaged by AJCC 7th Ed. for comparison ("New Stage"). DSS was adjusted for gender, age, race, histology, grade, ER, PR, surgery, chemotherapy, and radiotherapy using Cox methods with propensity score-based weighting and bootstrap standard errors. RESULTS: Among 924 patients having SI, 3.5% were men, and 8.7% Black. Tumors were 0.1-2.0 cm, 2.1-5.0 cm, and >5.0 cm in 11.6%, 51.1%, and 37.3% of cases, respectively (mean, 5.0 cm; median, 4.2 cm; range, 0.3 to 20.0 cm). There were no positive nodes in 22.3%, 1-3 positive in 31.7%, 4-9 positive in 28.6% and ≥10 positive in 17.4%. Cancers were 83.2% ductal, 8.3% lobular; 66.6% ER+ and 55.0% PR+ and 90.7% underwent mastectomies. For SI patients, adjusted 5 yr DSS was 98.1% for New Stage I and decreased to 33.2% for New Stage IIIC patients. Adjusted 5y DSS for SI did not differ from nonSI for New Stages I, IIA, and IIB, and was significantly lower for New Stages IIIA and IIIC (p=0.036 and p<0.001, respectively). Adjusted DSS for SI IIIA was similar to nonSI IIIC (see table). CONCLUSION: Noninflammatory breast cancers with SI have widely varied DSS and should not all be Stage III. As their prognosis is largely dependent upon tumor size and nodal involvement, we recommend that the SI status be added to TNM to group SI tumors with nonSI lesions having similar prognoses.

New Stage	SI Status	n (%*)	Unadjusted 5y DSS (%)	95% CI (%)	Adjusted 5y DSS (%)	95% CI (%)
I	nonSI	37,447 (56.6)	97.5	97.3-97.7	97.1	96.7-97.5
	SI	42 (4.5)	94.3	79.0-98.5	98.1	93.2-99.5
IIA	nonSI	17,100 (25.8)	92.8	92.3-93.3	92.6	91.6-93.4
	SI	127 (13.7)	84.7	75.1-90.8	89.2	80.6-94.2
IIB	nonSI	5,957 (9.0)	85.0	83.9-86.1	84.9	83.0-86.5
	SI	228 (24.7)	73.4	65.3-79.9	81.0	73.2-86.9
IIIA	nonSI	4,123 (6.2)	76.6	75.0-78.1	76.7	74.3-78.9
	SI	366 (39.6)	59.2	52.7-65.0	65.6	53.5-76.0
IIIB	Inflammatory and chest wall involvement excluded; SI reclassified					
IIIC	nonSI	1,558 (2.4)	60.4	57.5-63.2	60.5	56.9-64.0
	SI	161 (17.4)	36.7	26.9-46.5	33.2	23.4-44.7
* % of SI or nonSI cohort						

P8

The Use of Shave Margins Results in Lower Re-excision Rates During Breast Conservation Therapy C. Tokin,* B. Mailey, J. Baker, S. Hickey, A. Shaterian, S. Saba, S.L. Blair, A.M. Wallace. *University of California, San Diego, San Diego, CA.*

INTRODUCTION: Breast conservation therapy (BCT) has become the preferred method for treating early breast cancer. Clear surgical margins reduce the risk of local recurrence, and re-excision rates can vary widely between surgeons. Recent publications have shown at least a 20% re excision rate nationally for BCT across multiple institutions. We sought to assess our hospital-specific re-excision rate and to determine predictors for re-excision after BCT in light of adopting the shave margins technique (SCM). METHODS: Single institution retrospective review of patients with a diagnosis of carcinoma in situ or carcinoma of the breast between 2003-2011 was performed. Medical charts were reviewed to obtain demographic, clinical, histo-pathologic, and treatment data. All surgeons who participated used the SCM technique, and re-excisions were performed for close or positive margins RESULTS: A total of 1,715 breast cancers were diagnosed, and 1,091 underwent lumpectomy, resulting in a BCT rate of 63.62%. Of those who underwent initial lumpectomy, 9.62% (N=165) required re-excision for close (N=75) or positive (N=90) margins, 22 required more than one re-excision, and 41 eventually went on to mastectomy. 25% (N=42) received chemotherapy, 61% (N=101) received adjuvant radiotherapy, and 63% (N=104) received adjuvant hormonal therapy. On bivariate analysis, significant predictors of re-excision were histologic subtype (p=0.00), stage (p=0.019), grade (p=0.005), presence of LVI (p=0.001), hormone receptor status (p=0.023), and triple negative disease (p=0.028). On multivariate analysis, the only independent predictors of re-excision were age > 50 (OR= 0.5, p=0.14), lobular histology (OR=2.31, p=0.023), and high grade (OR=0.45, p=0.04). The local recurrence rate (LRR) was 1.2% with an average follow-up of 41.6 months. CONCLUSION: While younger age and lobular histology are risk factors for re-excision after BCT, we found high tumor grade as a negative predictive factor, specifically in the setting of using the SCM technique. With the increased use of BCT for breast cancer management, our low re-excision rate advocate for the use of SCM when performing lumpectomy.

P9

Bilateral Mastectomy: Is There a Social or Ethnic Factor Involved in Choice or Health Care Delivery? D. Yakoub,[1]* E. Avisar,[1] T. Koru-Sengul,[2] F. Miao,[1] M. Byrne,[2] F. Moffat,[1] A. Livingstone,[1] D. Franceschi.[1] *1. Department of Surgical Oncology, University of Miami-Miller School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL; 2. Department of Epidemiology and Public Health, University of Miami-Miller School of Medicine, Miami, FL.*

Introduction Bilateral mastectomy is an option for women who wish to reduce their risk of breast cancer or its recurrence. There has been concern about possible negative psychosocial sequelae following this procedure. However, few data are available regarding possible presence of disparity between patients undergoing the procedure. Methods Florida cancer registry and inpatient hospital data from the Agency for Health Care Administration (AHCA) were linked and queried for patients diagnosed with invasive breast cancer from 1996 to 2007. Primary end points were rate of bilateral mastectomy among races/ethnic origin and socioeconomic status (SES). Secondary end points were Marital and insurance status. Patients with diagnosed bilateral or multicentric breast cancer, and also patients with DCIS were excluded from the analysis. Results 55,228 Women were diagnosed with breast cancer between 1997 and 2007. 608 patients underwent bilateral mastectomy in the presence of a unilaterally diagnosed lesion. There were no significant differences between groups as to stage, grade or adjuvant treatment status. Patients identified themselves as White 76.3%, Black 7.1%, White Hispanic 11.5%, Black Hispanic 0.3% and other 2.2%. The rate of bilateral mastectomy was 78.1%, 5.4%, 12.5%, 0% and 2.4% in the same groups respectively (p<0.001). 60.3% of patients who had bilateral mastectomy were categorized as middle high and high SES as compared to 34.5% as low SES (p<0.001). 95.2% lived in urban areas while 4.8% lived in rural areas by zip code (p<0.001). 86% were currently or previously married while 12.2% were never married. 76.6% had private insurance or Medicare, 5.9% had Medicaid or noninsured (P<0.001). Conclusion Bilateral mastectomy rate showed significant disparities among patients of different race/ethnicity, socioeconomic class, marital status and insurance coverage. This observation is not accounted for by population distribution, incidence or disease stage. More in-depth study of the causes of these disparities in healthcare choice and delivery is critically needed.

P10

Differences in Prognostic Significance of Axillary Lymph Node Status in Patients with High Grade Breast Cancer According to Biological Subtypes of Tumors B. Chikman,[1] R. Lavy,[1]* L. Habler,[2] J. Sandbank,[2] A. Halevy.[1] *1. Assaf Harofeh Medical center i, Tel Aviv, Israel; 2. Institute of Pathology Assaf Harofeh Medical Center, Tel aviv, Israel.*

Background: The prognostic significance of biological subtypes of breast cancer is well known. The status of the axillary lymph nodes is another well known predictor for outcome. The aim of this study was to estimate patient prognosis according to the lymph node status in different biological subtypes of breast cancer. Methods: 303 patients with high grade infiltrating duct carcinoma (grade 3) without previous neo-adjuvant therapy were selected and

served as the basis for this study. Biological subtypes of breast cancer were determined according to immunohistochemical staining for ER, PR and Her2 as follows: luminal A (ER+ or PR+ and HER-2–), luminal B (ER+ or PR+ and HER-2-),HER-2 over expressing (ER– and PR– and HER-2+), and triple negative (ER– and PR– and HER-2. Results: Our series was composed of 303 patients with high grade breast cancer .276/303 patients (91.1%) underwent axillary surgery. Distribution according to biological subtypes was: luminal A 156/303 (51.5%), luminal B 56/303 (18.5%), HER-2 over expressing 26/303 (8.6%) and triple negative 65/303 (21.5%). The rate of lymph node involvement in each group was: 48.9%, 52.8%, 45.8% and 40.3% correspondently. In the group of patients with negative axillary lymph nodes we did not find significant differences in recurrence rate among patients with favorable luminal A type and other biological subtypes. The disease progression in this group of patients was as follow: 11.4%, 4.0%, 15.4% and 14.9%, correspondently. The biological pattern of the primary tumor has more prominent prognostic significance in the group of patients with positive lymph nodes. Disease progression was documented in 28.4%%, 42.9%, 81.8% and 40.0%, correspondently. Conclusion: Previous studies found that the biological patterns of breast cancer have a strong influence on the outcome. In our study on the group of patients with high grade breast cancer we showed that the differences in outcome are significant only in the subgroup of patients with positive lymph nodes.

P11

Lack of Lymph Node Evaluation in Early Stage Breast Cancer: Epidemiology and Survival A.K. Arrington,* C. Vito, L. Kruper, J. Yim, S.L. Chen. *City of Hope, Duarte, CA.*

Background: Lymph node evaluation (LNE) is a key component in breast cancer staging. There are a number of breast cancer patients that do not have surgical LNE. We sought to describe the prevalence of this phenomenon. We hypothesized that these patients would be less likely to receive other indicated care such as radiation therapy. Methods: The SEER registry was used to identify patients with invasive ductal/lobular breast cancer from 1998-2009. Inclusion criteria included patients >18yo with a single Stage I/II breast cancer. Logistic regression was used to analyze factors correlating with lack of LNE. Inappropriate omission of radiation therapy (RT) was defined as those not having radiation therapy recommended and had LNE omitted, those who undergo a lumpectomy, or mastectomy performed for size>5cm or T4 disease. Cox Regression was utilized for multivariate analysis. Survival comparisons were made to patients likely to be clinically node negative defined as N0 patients or with <2cm lymph node metastases. Results: 21,570 out of 302,629 eligible patients (8.1%) did not undergo a LNE. Of those without LNE, 76.7% underwent a lumpectomy. Patients who did not have LNE were more likely to be older (>70), single, rural, and have smaller tumors ($p<0.001$). Hormone receptor status and type of surgery performed were not significant factors. Only 74.5% of patients without LNE had appropriate adjuvant RT, compared to 88.7% of those undergoing LNE ($p<0.001$). After adjustment for other factors, survival was decreased in patients without LNE as compared to those undergoing LNE (HR=2.19, 95%CI 2.15-2.26). In a subset of age>70 and T1 tumors, the same decrease in survival was seen. (HR=2.2, 2.1-2.29). Conclusion: LNE is generally recommended in early stage breast cancer, but there continues to be a significant percentage who do not undergo LNE. This is more common in older patients with smaller tumors; however, 3.7% of the youngest patients with larger tumors had LNE omitted. Survival is decreased in this broader group. While this may represent case selection bias, omission of LNE in smaller tumors and its impact on survival may merit further study in a more controlled setting.

P12

Patterns of Lymphedema Risk Reducing Behaviors in Clinical Practice after Axillary Lymph Node Surgery S.A. McLaughlin,* S. Koonce, T. Gibson, N. Diehl, J. Crook, S. Bagaria, J. Nguyen. *Mayo Clinic, Jacksonville, FL.*

Introduction: Despite widespread patient adoption of risk reducing behaviors (RRB) to prevent lymphedema, clinicians disagree on their value. Further, practice implementation is frequently synonymous only with prior breast cancer treatment. We hypothesized that variations exist in clinician recommendations for RRB and that application is dependent on clinician training and disease type. Methods: We invited 1750 physicians and nurses at our institution to participate in an intranet based survey evaluating scenarios questioning the acceptability of IV placement, blood pressure, or venipuncture in the ipsilateral upper extremity after axillary node surgery. The response rate was 722/1750 (41%). Using Fisher's Exact and McNemar's tests we analyzed survey responses according to professional training and disease subgroup. Results: The 722 respondents were comprised of 219 (30%) physicians, 497 (69%) nurses, and 6 (1%) unspecified clinicians of whom 455/722 (63%) had >10yrs clinical experience. Overall, clinicians favor implementation of RRB more commonly after breast cancer than melanoma treatment (92% vs 85%, $p<0.001$) and less commonly after axillary lymph node biopsy for lymphoma diagnosis (68%, $p<0.001$). Among breast cancer patients, clinicians discriminate need but still recommend RRB by axillary surgery (63% after SLN vs 92% after ALND, $p<0.001$) and breast surgical procedure (63% after BCT vs 85% after mastectomy, $p<0.001$). At 5 yrs post breast cancer surgery, 67% of clinicians still felt it was inappropriate to place an IV in the ipsilateral arm. Years in clinical practice did not correlate with application of RRB in any scenario (all $P>0.06$) however nurses were significantly more likely than physicians to recommend RRB in all scenarios, 76% (95% CI 72-79%) vs 47% (95% CI 40-53%) respectively. In total 34% of respondents cite historical teachings as the primary reason for enforcing RRB. Conclusion: Health care professionals lack evidence based guidelines and therefore inconsistently apply RRB. Future studies exploring RRB should interrogate their value and explore practice standardization based on the nodal procedure only regardless of disease entity.

P13

Referral Patterns of Ontario General Surgeons to Plastic Surgeons for Breast Reconstruction J. Platt,[1]* T. Zhong,[4] G. Booth,[6] A. Easson,[4] K. Fernandes,[2] R. Moineddin,[3] N. Baxter.[5] *1. Division of Plastic and Reconstructive Surgery, University of Toronto, Toronto, ON, Canada; 2. Institute for Clinical and Evaluative Sciences, Toronto, ON, Canada; 3. Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada; 4. University Health Network, Toronto, ON, Canada; 5. Department of Surgery and Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; 6. Department of Medicine, University of Toronto, Toronto, ON, Canada.*

Introduction: General surgeon referral to plastic surgery has been identified as a rate-limiting step for breast reconstruction (BR) among breast cancer patients. This study proposes to explore the general surgeon and institution factors associated with referral patterns. Methods: This is a retrospective analysis of population-based administrative data in Ontario, Canada. Women aged 18 through 65 years who underwent incident mastectomy from 2002 to 2007 were identified and classified as having BR within 3 years of mastectomy or mastectomy alone. This study examined the cohort of general surgeons who performed mastectomy and plastic surgeons who performed BR. The outcome of interest was the rate of referral for BR. We used generalized estimating equations following a Poisson distribution to examine the association of general surgeon and institution characteristics with this outcome. Results: 455 general surgeons were eligible. The median referral rate was 14.2% (interquartile range 0 to 28.6%). The majority of general surgeons (n = 324, 71.2%) referred at least 1 patient. Of those who referred >= 1 patient, 33.6% referred >= 5 patients and 56.5% referred to >= 2 different plastic surgeons. Factors examined are reported in table 1. Multivariable Poisson regression suggested that surgeons who practice in communities with >= 1.5 million people were 2.21 times more likely to refer an additional mastectomy patient for BR (95% confidence interval [CI] 1.42 to 3.43, p = 0.0004), and those from communities of 100,000 to 1,499,999 were 1.92 times (95% CI 1.24 to 2.95, p = 0.0032) more likely. Female general surgeons had a 1.46 times greater referral rate (95% CI 1.13 to 1.88, p = 0.0031). Availability of a plastic surgeon within the same institution was not a significant predictor. Conclusion: This study showed that community size of a general surgeon's practice, and not local availability of a plastic surgeon within the same institution, is associated with patient referral to a plastic surgeon for BR. Understanding of the influence of geography as it pertains to referral patterns, in particular the influence of regional plastic surgeon availability, warrants further study.

Table 1: Association between general surgeon and institution factors and general surgeon referral indices.

	Unadjusted Odds of Referring at Least 1 Patient			Adjusted Model for Referral Rate		
	OR	95% CI	p-value	RR	95% CI	p-value
General Surgeon Variables						
Demographics						
Age	0.88*	0.80 to 0.97	0.0073			
Sex						
Female	1.52	0.85 to 2.72	0.15	1.46	1.13 to 1.88	0.0031
Male	Ref	-	-	Ref	-	-
Practice Characteristics						
Years in Practice	0.87*	0.80 to 0.96	0.0011	1.00*	0.96 to 1.05	0.97
Geographic Factors						
Community Size						
1,500,000+	2.74	1.63 to 4.63	0.0001	2.21	1.42 to 3.43	0.0004
100,000 to 1,499,999	2.59	1.59 to 4.24	0.0001	1.92	1.24 to 2.95	0.0032
< 100,000	Ref	-	-	Ref	-	-
Institutional Factors						
Hospital Status						
Teaching and/or Cancer Centre	1.99	1.22 to 3.24	0.0051	1.13	0.88 to 1.45	0.35
Community Hospital	Ref	-	-	Ref	-	-
Local plastic surgeon						
Yes	2.07	1.37 to 3.14	0.0005	1.06	0.82 to 1.38	0.67
No	Ref	-	-	Ref	-	-
Annual number of breast cancer related procedures	1.27***	1.11 to 1.26	< 0.0001	0.98***	0.91 to 1.06	0.65

Legend: CI = confidence interval; * units are in 5 year increments; ** units are for every 10 additional procedures at the surgeon level; *** units are for every 50 additional procedures at the institutional level. ^ Generalized estimating equations with Poisson distribution were used to adjust for correlated outcomes within institutions.
Age and years in practice were collinear in the model. Interaction terms were tested and not significant.

P14

Surgical versus Hormonal Therapy in Breast Cancer Patients Aged >80 years A. Perhavec,* J. Zgajnar, M. Hocevar, N. Besic. *Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia.*

Background Breast cancer (BC) patients (pts) aged >80 years often receive only hormonal therapy (HT) and there are data that such treatment might not be optimal. The aim of our retrospective study was to compare the overall and BC specific survival of BC pts aged >80 years who were surgically treated with those who received HT only. Pts and methods All together 282 BC pts aged >80 years were treated at our Institute from January 2000 to December 2005. Pts with metastatic disease at presentation (17) and pts that received other treatment modalities besides surgery and HT (chemotherapy 5, radiotherapy 20) were excluded from this analysis. 240 pts were included in the present study. Cox regression model was used to determine the correlation of surgical therapy with overall and BC specific survival. Other covariates included in the model were age, ASA value (physical status classification system), performance status, tumor and nodal stage. Results Of 240 pts included in the study, 161 (67%) received HT only and 79 (33%) were surgically treated. Of those who were surgically treated, 70 (89%) received also pre- and/or postoperative HT. The mean age of pts in the HT and surgery arm was 85.5 and 82.6 years, respectively ($p<0.001$). 5-year overall and BC specific survival of all 240 pts was 39 and 72%, respectively. 5-year overall survival of pts who received HT only and those who were surgically treated was 27.5 and 64%, respectively. 5-year BC specific survival of pts who received HT only and those who were surgically treated was 63 and 84%, respectively. In multivariate Cox regression model five variables predicted overall survival (surgery (HR 2.9), age (HR 1.1), tumor (HR 1.2) and nodal (HR 1.6) stage and ASA value (HR 1.6)) and four variables predicted BC specific survival (surgery (HR 2.1), tumor (HR 1.4) and nodal (HR 2.0) stage and performance status (HR 1.7)). Conclusion Our study shows that both overall and BC specific survival are better in surgically treated BC pts aged >80 years compared to those who received HT only.

P15

The Influence of Sentinel Node Breast Cancer Metastasis Size on Systemic Metastases and Survival in Patients with cN0 disease R. Shah,* D.S. Nathanson, D. Chitale, M. Mahan. *Henry Ford Health System, Detroit, MI.*

Introduction: cN1, cN0/pN2 or N3 breast cancer (BC) is more likely to metastasize to systemic sites (SysMets) than cN0/pN1 or cN0/pN0. Despite information that axillary tumor burden influences the likelihood of SysMets very little is known about how sentinel lymph node metastasis size (SLNMS) affects metastasis. We hypothesized that increasing SLNMS would be associated with a higher rate of SysMets and a higher mortality. Methods: Demographic, clinical and pathologic data from cN0 breast cancer patients (1995 through 2011) was retrospectively analyzed. Median and mean follow-up times for all patients were 54 and 59.7 months, respectively. Overall and disease-specific survival was determined by Kaplan-Meier and regression analysis was performed with particular attention to SLNMS and SLN size. Results: Of 1804 evaluable patients that had SLN biopsy 370 (20.5%) were SLN positive and 257 SLNMS were analyzed. SLNMS was 11.6mm (± 9.5) vs 7.8mm (± 9.1) in 30 patients with SysMets vs. 227 patients without ($p = 0.017$). Every 1 mm increase in SLNMS increased the odds of SysMets by 1.036 (95% CI: 1.001, 1.072; $p=0.0436$). The larger the ratio SLNMS/SLN size the greater the odds of systemic metastasis (OR 3.45 (95% CI 1.18, 10.07; $p= 0.024$). Multivariate logistic regression confirmed that tumor size (OR 1.03 (95% CI: 1.02, 1.04; $p<0.001$) and ER negative receptor status (OR 2.16 (95% CI 1.43, 3.28; $p <0.001$) lead to higher odds of SysMets. Conclusion: The greater the SLNMS and SLNMS/SLN ratio the more likely breast cancer is to metastasize systemically. This confirms the relationship between metastases and axillary tumor burden in cN1 and cN0/pN1, pN2 and pN3. Patients with larger ER negative tumors, more likely to die from breast cancer metastases, are even more likely to have SysMets when they have large SLNMS.

Illustrating the SLN met size and SLN ratio as a predictor of systemic metastases

	N		Systemic metastasis-No	N	Systemic metastasis-Yes	P-Value
SLN met size (mm)	227	Mean ± SD	7.8mm (± 9.1)	30	11.6mm (± 9.5)	0.017
		Median (Min, Max)	4mm (0, 70)		10 mm (0.5, 40)	
SLN ratio	206	Mean ± SD	0.4 (0.3)	29	0.6 (0.4)	0.024
		Median (Min, Max)	0.2 (0, 1.0)		0.5 (0, 1.0)	

P16

Sub-Areolar Tissue Specimen Assessment in Nipple Sparing Mastectomies. A Preliminary Analysis of the American Society of Breast Surgeons Nipple Sparing Mastectomy Registry S.D. Mitchell,[1]* P. Beitsch,[2] S. Willey,[3] S.M. Feldman,[4] D.E. Manasseh,[5] G. Unzeitig.[6] *1. Surgery, White Plains Hospital Medical Center, White Plains, NY; 2. Dallas Breast Center, Dallas, TX; 3. Georgetown, Washington DC, DC; 4. Columbia Univer-sity College of Physicians & Surgeons, New York, NY; 5. Maimonides Medical Center, New York, NY; 6. Laredo Breast Care, Laredo, TX*

Intro: The ASBS NSMR is an ongoing, prospective, non-randomized, IRB approved, multi-institutional registry assessing utilized metrics and techniques as well as aesthetic and oncologic outcomes of NSMs. Methods: We assessed utilization of intraoperative sub-areolar (SA) pathology results, as well as action taken. This is a preliminary analysis of the first 320 mastectomies entered into the American Society of Breast Surgeons (ASBS) Nipple Sparing Mastectomy Registry (NSMR). NSMs were performed on 207 patients (320 mastectomies), by 37 investigators at 35 institutions of which 83 (26%) were for invasive cancer, 46 (14%) for DCIS, and 191 (60%) were prophylactic. Results: Intraoperative SA pathology assessment was requested on 104 (33%) of mastectomies. Indications for these mastectomies were invasive cancer (41), DCIS (28) and prophylaxis (35). Intraoperative pathology of the SA specimens included: No Evidence of Disease (NED) (98), Indeterminate (2), Cancer (1), Suspicious for cancer (1), and Other (2). Final SA pathology results were NED (101) and DCIS (3). Out of the 3 specimens with final path results of DCIS: indication for mastectomy was DCIS (3) and intraoperative assessment path results were cancer (2) and NED (1). Of the 216 mastectomies without intraoperative SA pathology, there was one positive SA pathology (DCIS) resulting in a NAC resection. None of the final pathology results for SA specimens yielded invasive carcinoma. Tumor size ranged from 1cm-7cm, and distance from tumor to NAC ranged from 1.6-4.1cm (measured via clinical, US, MMG, and MRI). Conclusions: Two NACs (2%) were unnecessarily excised secondary to preliminary intraoperative SA path results and only one patient (0.5%) who did not have intraoperative pathology had to return for NAC removal. The potential of false positive intraoperative pathology and subsequent removal of an unaffected NAC render the use inappropriate. The risk of obtaining intraoperative sub-areolar path appears to outweigh the benefit of finding a positive intraoperative SA pathology and avoiding an unnecessary NAC excision.

P17

Impact of Molecular Subtype on Locoregional Recurrence in Mastectomy Patients with T1-2 Breast Cancer and 1-3 Positive Lymph Nodes T. Moo,[1]* R. McMillan,[1] M. Lee,[2] M. Stempel,[1] A.Y. Ho,[1] S. Patil,[1] M. El-Tamer.[1] *1. Memorial Sloan-Kettering Cancer Center, New York, NY; 2. Weill Cornell Medical College, New York, NY.*

Introduction Postmastectomy radiation (PMRT) in T1-T2 tumors with 1-3 positive lymph nodes is controversial; the impact of molecular subtype (MST) on locoregional recurrence (LRR) and PMRT benefit is uncertain. We examined the association between MST and LRR in this group. Methods In a prospectively maintained institutional database, we identified all patients who underwent modified radical mastectomy between 1995-2006. Patients receiving neoadjuvant chemotherapy, T3-4 tumors or >3 positive lymph nodes (LNs) were excluded. MST was defined as: hormone receptor (HR) positive/HER2- (Luminal A/B), HR+/HER2+ (Luminal HER2), HR-/HER2+ (HER2), and HR-/HER2- (basal). The Kaplan-Meier method and Cox regression analysis were used to examine the association between MST and LRR, recurrence-free survival (RFS), and overall survival (OS). Results 884 patients (700 no PMRT, 141 PMRT) were included, with 72.9% luminal A/B, 7.8% luminal HER2, 6.8% HER2, and 12.5% basal. Median follow-up was 7 years; 39 LRRs occurred. There was no difference between the subtypes in receipt of PMRT (p=0.39). As expected, there were differences in clinicopathologic variables among the subtypes. The luminal A/B subtype had the smallest tumor size (p=0.03), and the lowest intraductal component (p=0.01), histologic/nuclear grade (p<0.0001), lymphovascular invasion (LVI) (p=0.008) and multifocality/multicentricity (p=0.02). On univariate analyses, MST was associated with RFS and OS, with the basal and HER2 subtype having the lowest RFS (p=0.0002) and OS (p<0.0001). On multivariate analysis, age ≤50 years (p=0.002) and presence of LVI (p=0.0003) were predictive of LRR; MST was not (p=0.38). Although MST was not associated with LRR in the entire cohort, analysis in patients who received PMRT showed an association between MST and LRR (p=.05). MST was not associated with LRR in the no-PMRT group (p=0.35). Conclusions In patients with T1-2 breast cancer and 1-3 positive lymph nodes who did not receive PMRT, MST was not a predictor of LRR and may not be useful in selecting PMRT candidates in that group.

Table 1. Comparison of 5-year LRR-free survival and RFS by subtype

Subtype (n)	5-year LRR-free survival		5-year RFS
	PMRT (95% CI)	No PMRT (95% CI)	Overall RFS (95% CI)
Luminal A/B (644)	0.98 (0.92-0.99)	0.96 (0.94-0.97)	0.87 (0.84-0.90)
Luminal HER2 (69)	1.00	0.96 (0.85-0.99)	0.81 (0.69-0.89)
Basal (111)	0.98 (0.92-0.99)	0.94 (0.85-0.98)	0.72 (0.55-0.79)
HER2 (60)	0.83 (0.48-0.95)	0.93 (0.80-0.97)	0.69 (0.55-0.79)
	p=0.04	p=0.35	p=0.0002

LRR, locoregional recurrence; RFS, recurrence-free survival; PMRT, postmastectomy radiation; CI, confidence interval

P18

Radioactive Seed Localization Compared to Wire Localization in Breast-Conserving Surgery: Initial 6-Month Experience J.O. Murphy,* T. Moo, T.A. King, K.J. Van Zee, K.A. Villegas, M. Stempel, A. Eaton, E. Morris, M. Morrow. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction Wire localization (WL) of non-palpable breast cancers performed on the day of surgery is uncomfortable for patients and impacts OR efficiency. Radioactive seed localization (RSL) prior to the day of surgery avoids these disadvantages. In this study we compare outcomes of our initial 6-month experience with RSL to those with WL in the preceding 6 months. Methods Lumpectomies for invasive or intraductal cancers localized with a single ^{125}iodine seed (January-June 2012) were compared to those using 1 wire (July-December 2011). Surgeons and radiologists did not change between study periods. Positive and close margins were defined as tumor on ink and tumor ≤1mm from ink, respectively. Demographic and clinical factors, and outcomes were compared between patients treated with RSL and WL using Fisher's exact test for categorical covariates and Wilcoxon tests for continuous covariates. Results There were 431 RSL and 256 WL lumpectomies in the study period. Patient age, tumor size, and the presence of ductal carcinoma in situ did not differ between groups (Table). Seeds were placed a median of 1 day pre-op (range, 0-47). Positive margins were present in 7.7% of RSL vs. 5.5% of the WL group, and 16.9% of RSL vs. 19.9% of WL had close margins (p=0.38). Operative time was significantly longer in the RSL group (median time, 50 vs. 45 minutes; p=0.003). There was no significant difference in excision volume between groups with a median excision volume of 21.5 cm^3 for RSL vs. 19.2 cm^3 for WL (p=0.096). Conclusions In the first 6 months of RSL, rates of positive and close margins were similar to those seen after many years of experience with WL. Operative time was slightly longer for RSL during the learning phase. We anticipate this will decrease with experience. We believe the use of RSL can simplify operative scheduling and improve patient comfort without negatively impacting upon outcomes.

Table. Patient and Tumor Characteristics of the Seed Localization and Wire Localization Groups

Characteristic	Seed (N=431)	Wire (N=256)	p-value
	No. (%)	No. (%)	
Age (yrs), median (range)	59 (26-92)	60 (30-86)	0.3124
Tumor type:			
Infiltrating ductal	261 (60.6)	169 (66.0)	0.2794
Infiltrating lobular	43 (10.0)	18 (7.0)	
Infiltrating, other	24 (5.6)	11 (4.3)	
DCIS + microinvasion	11 (2.6)	11 (4.3)	
DCIS	92 (21.3)	47 (18.4)	
Infiltrating carcinoma:	(N=328, 76.1%)	(N=198, 77.3%)	
Pathological T stage:			
T1	300 (91.5)	175 (88.8)	0.3201
T2	28 (8.5)	22 (11.1)	
Tumor size (mm), median (range)	11.0 (1.0-41.0)	11.0 (1.5-30.0)	0.4384
Presence of DCIS:			
Limited DCIS present	231 (70.4)	147 (74.2)	0.4390
Extensive intraduct component	21 (6.4)	16 (8.1)	
DCIS (+/- microinvasion):	(N=103, 23.9%)	(N=58, 22.7%)	
Radiological extent (mm), median (range)	8.0 (2.3-55.0)	10.0 (1.0-50.0)	0.4907
Margin status:			
Clear	324 (75.2)	191 (74.6)	0.3827
Tumor on ink	33 (7.7)	14 (5.5)	
Close (tumor ≤ 1mm from ink)	73 (16.9)	51 (19.9)	
Reoperation to improve margins	99 (23.0)	57 (22.3)	0.8313
Operative time (mins), median (range)	50 (16-167)	45 (12-105)	0.0026
Lumpectomy volume (cm^3), median (range)	21.5 (0.2-311.2)	19.2 (0.9-197.9)	0.0958

DCIS, ductal carcinoma in situ

P19

Immediate Reconstruction in Asian American Women after Mastectomy: Trends and Disparities B.A. Wexelman,* D.Y. Lee, A. Estabrook, A.T. Ma. *Surgery, St Luke's Roosevelt Hospital, New York, NY.*

Introduction: It has been shown in regional studies that Asian American women with breast cancer undergo reconstruction after mastectomy at lower rates than other demographic groups. We seek to determine if disparities exist nationally in immediate reconstruction for Asian American women after mastectomy. Methods: We compared socioeconomic and geographic features for 14,986 women who underwent mastectomy in 2008 using the Nationwide Inpatient Sample, an all-payer stratified statistical sample of all US hospital discharges. Asian Americans (n=473) were compared to the national sample, and reconstruction was classified into three groups: patients without reconstruction (NR), breast implant/ tissue expander reconstruction (TE), and advanced reconstruction techniques such as free or pedicled flaps (FLAP). Results: Asian women were less likely to undergo reconstruction (66.9% non- reconstructed) after mastectomy than the national cohort (63.9%). Asian mastectomy patients were younger (56.5 yrs vs. 60.0 yrs, p<0.001) and healthier (2.86 vs. 3.41 comorbid conditions, p<0.001), with decreased length of stay (2.03 vs. 2.21 days, p=0.12). Asians were less likely to have advanced FLAP reconstructions (10.3% vs. 12.2%) and tissue expander/ implant reconstructions (22.9% vs 23.9%). However, they were more likely to have private insurance (60.0% vs. 51.3%, p<0.001) and higher average incomes. Asian breast cancer patients were much more likely to live in a major city (>1 million people) than the national sample (68.2% vs. 29.7%, p<0.001). The states with the highest numbers of Asian women undergoing FLAP reconstruction were California, New York, New Jersey, Massachusetts, and Texas. Conclusions: Asian women undergoing mastectomy for breast cancer are younger, healthier, and have private insurance at higher rates than women nationally- yet they obtain immediate breast reconstruction at lower rates, especially advanced flap techniques. Further research needs to be done to understand if patient preference or barriers to access to reconstruction are the cause of these disparities.

Trends in Immediate Reconstruction after Mastectomy: Asian Americans compared to National Cohort

		National Cohort (%)	Asian Americans (%)	p Value
N		14,513	473	
Age (years)		60.03	56.47	<0.001
Comorbid Conditions (number)		3.41	2.86	<0.001
Length of Stay (days)		2.21	2.03	0.12
Hospital Charges ($)		30389.43	33451.61	0.015
Reconstruction Type	No Reconstruction	9128 (63.9)	313 (66.9)	0.313
	Tissue Expander/ Implants	3419 (23.9)	107 (22.9)	
	FLAP Reconstruction	1749 (12.2)	48 (10.3)	
Insurance	Medicare	5411 (37.3)	122 (25.8)	<0.001
	Medicaid	1025 (7.1)	51 (10.8)	
	Private inc HMO	7439 (51.3)	284 (60.0)	
	Self Pay	179 (1.2)	11 (2.3)	
	No Charge	64 (0.4)	1 (0.2)	
	Other	386 (2.7)	4 (0.8)	
Median Income for Zipcode	$1- $39K	3157 (22.1)	39 (8.4)	<0.001
	$39K- $48K	3547 (24.9)	58 (12.5)	
	$48- 63K	3478 (24.4)	116 (24.9)	
	$63K +	4077 (28.6)	252 (54.2)	
Location	>1Mill	4077 (29.7)	303 (68.2)	<0.001
	Fringe of City >1M	3341 (24.4)	87 (19.6)	
	Metro 250K - 999K	2588 (18.9)	43 (9.7)	
	50-250K	1283 (9.4)	5 (1.1)	
	Micropolitan counties	1428 (10.4)	5 (1.1)	
	Not metro/micro	994 (7.2)	1 (0.2)	

P20

Human Epidermal Growth Factor Receptor 2 (HER-2) Pulsed Type I Dendritic Cells (DC) Induce T cell and Clinical Responses in Early Breast Cancer (BC) Patients Independent of Tumor HER-2 Expression Levels M.E. Fracol,* S. Xu, R. Mick, E. Fitzpatrick, H. Nisenbaum, C. Fisher, P.J. Zhang, B.J. Czerniecki. *University of Pennsylvania, Philadelphia, PA.*

Background: Despite advent of trastuzumab, HER-2 expressing BC pts are at higher risk for local and systemic recurrence. Several vaccines in development for pts with HER-2 expressing BC have suggested diminished recurrence following vaccinations in low expression HER-2 (1+ or 2+) pts, while high expression HER-2 (3+) pts are less likely to have a positive clinical outcome. We investigated whether different clinical response rates between HER-2 (2+) and (3+) pts holds true in our HER-2 pulsed DC vaccine trials by measuring tumor presence and HER-2 status post-vaccination. We also compared CD4 and CD8 T cell response rates. Methods: 48 Pts with DCIS or T1a HER-2 expressing BC received either 4 weekly lymph node injections in the groin or 6 weekly injections in the area of DCIS or groin nodes prior to surgical resection of tumor. HER-2 expression was determined by IHC staining pre- and post-vaccination. In 44 pts, CD4 T cell sensitization to 6 HER-2 peptides was determined by ELISPOT assay and a positive response was defined by >2-fold increase post-vaccination. In 21 pts, CD8 T cell response was determined by in vitro sensitization. Results: There was no significant difference in complete tumor regression rates between 12 HER-2 (2+) and 36 HER-2 (3+) pts (25.0% vs 16.7%, p=0.67). HER-2 (2+) pts were significantly more likely to eliminate HER-2 expression post-vaccination than HER-2 (3+) pts (75.0% vs 8.3%, p=0.000023). Overall 40/44 (90.9%) pts developed CD4 T cell responses to HER-2 peptide and CD4 responses were equally likely in HER-2 (2+) and (3+) pts (81.8% vs 93.9%, p=0.56). Overall 18/21 (85.7%) HLA A2+ pts developed CD8 T cell immune responses to HER-2 and CD8 T cell responses were equally likely in HER-2 (2+) and (3+) pts (75% vs 88.2%, p=1.0). Conclusion: HER-2 pulsed type I DC vaccines induce T cell and clinical responses in both HER-2 (2+) and (3+) pts. These vaccines can be developed as adjuvants for use in preventing recurrence in pts with both intermediate and high expressing HER-2 BC.

HER-2 (2+) and (3+) Patients' T Cell and Clinical Response Post-Vaccination

HER-2 Pre-Vaccine Expression Level	Complete Tumor Regression (n=12)	Elimination of HER-2 Expression (n=12)	Positive CD4 T Cell Response (n=11)	Positive CD8 T Cell Response (n=4)
HER-2 (2+)	3 (25%)	9 (75%)*	9 (81.8%)	3 (75%)
	Complete Tumor Regression (n=36)	Elimination of HER-2 Expression (n=36)	Positive CD4 T Cell Response (n=33)	Positive CD8 T Cell Response (n=17)
HER-2 (3+)	6 (16.7%)	3 (8.3%)*	31 (93.9%)	15 (88.2%)

*statistically significant difference, p=0.000023

P21

Novel Factor to Improve Prediction of Node Positivity in Patients with Clinical T1/T2 Breast Cancer T.A. Torstenson,[1]* M. Shahkhan,[1] T. Hoskin,[2] S. Chartier,[1] J. Case,[1] M. Morton,[1] J.C. Boughey.[1] *1. Mayo Clinic Surgery Department, Rochester, MN; 2. Mayo Clinic Biostatistics, Rochester, MN.*

Introduction: Prediction of nodal positivity can guide surgical planning in breast cancer patients. Both Memorial Sloan Kettering Cancer Center (MSKCC) and MD Anderson Cancer Center (MDACC) have established nomograms to predict risk of sentinel node positivity. We propose that the addition of distance of tumor from the nipple can improve their performance. Methods: With IRB approval women with clinical T1/T2 tumors who underwent pre-biopsy ultrasound from 02/2009 to 12/2011 were reviewed. Ultrasounds were re-reviewed to measure tumor distance from the nipple. MSKCC and MDACC nomogram predictions were calculated and the AUC-ROC for each model calculated. The added utility of this variable was then examined using multiple logistic regression and by comparison of AUC-ROC values. Results: 401 breast cancers with clinical T1 (85%) or T2 (15%) tumors in 398 patients met eligibility criteria, of which 79/401 (19.7%) were found to be node positive. Tumors were significantly closer to the nipple in those with positive nodes as compared to negative nodes. 17/33 (51.5%) tumors within 2 cm of the nipple were node positive versus 62/368 (16.8%) tumors >2 cm from the nipple (p<0.0001). The MSKCC and MDACC nomograms each demonstrated good discrimination between node positive and negative patients with AUC-ROC values of 0.71 (95% CI: 0.64-0.77) and 0.74 (95% CI: 0.68-0.81), respectively. When added to the MSKCC nomogram, distance from nipple ≤2 cm contributed significantly (odds ratio 4.78, p=0.0001) to the prediction of node positivity and improved the AUC-ROC to 0.73 (95% CI: 0.67-0.80). Similarly, distance from nipple ≤2 cm was significant (odds ratio 4.73, p=0.0002) when added to the MDACC nomogram and improved the AUC to 0.76 (95% CI: 0.70-0.82). Within nomogram probability categories, the proportion with positive nodes was consistently higher in the subgroup with distance from nipple ≤2 cm (Table 1). Conclusions: Tumor distance from the nipple is associated with nodal positivity. When added to nomograms it improves the prediction of node positivity. This variable should be considered in estimating nodal positivity and treatment planning for breast cancer.

Table 1. Proportion with positive nodes in subgroups based on nomogram predicted probabilities and distance from nipple.

MSKCC nomogram predicted probability	Distance from nipple	N (%) with positive nodes
<25%	≤2cm	6/17 (35%)
<25%	>2cm	27/249 (11%)
25-49%	≤2cm	8/13 (62%)
25-49%	>2cm	28/97 (29%)
≥50%	≤2cm	3/3 (100%)
≥50%	>2cm	7/22 (32%)
MCACC nomogram predicted probability	Distance from nipple	N (%) with positive nodes
<25%	≤2cm	11/26 (42%)
<25%	>2cm	47/330 (14%)
25-49%	≤2cm	5/6 (83%)
25-49%	>2cm	14/35 (40%)
≥50%	≤2cm	1/1 (100%)
≥50%	>2cm	2/3 (67%)

P22

A Comparison in Clinical Outcomes Between Oncoplastic Reduction and Standard Lumpectomy for Breast Cancer M.K. Miller,[1]* J.R. Dietz,[1] A.A. Fanning,[2] J.P. Crowe,[2] C. O'Rourke,[2] R.J. Yetman,[3] S.A. Valente.[2] *1. Cleveland Clinic, Cleveland, OH; 2. Cleveland Clinic, Cleveland, OH; 3. Cleveland Clinic, Cleveland, OH.*

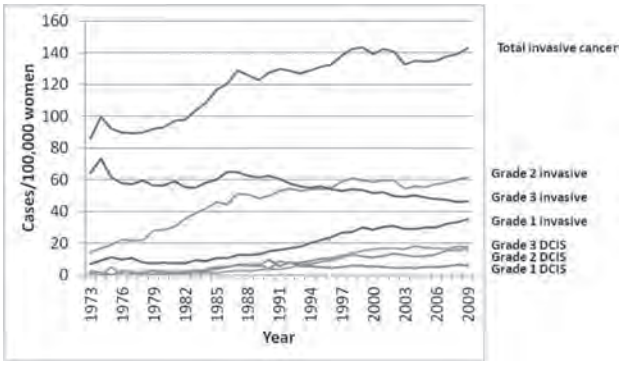
Background: Oncoplastic reduction has recently been shown to be an effective local treatment for breast cancer in large breasted women. There is little data comparing this technique to standard lumpectomy in this cohort. The purpose of this study was to compare the outcomes of large breasted patients with breast cancer treated with Oncoplastic Reduction to that of Standard lumpectomy with regards to rates of re-excision, locoregional and distant recurrence, and completion mastectomy. Methods: An IRB approved retrospective chart review of 71 large breasted patients treated for breast cancer at a single institution between 2005 and 2012 was conducted. Using the modified Katariya formula, breast volumes were calculated using mammographic images to identify the control group for comparison to the reduction oncoplastic group. Each

group was evaluated for demographics. Results: The two groups were found to be similar with regards to age and BMI. Patients with an average breast volume of 1074 cubic cm who underwent oncoplastic reduction had a 5.7 % reexcision rate, 2.8 % local regional recurrence rate and 2.8 % distant recurrence rate. In contrast, patients with similar breast volumes who underwent the traditional standard lumpectomy had reexcision rates significantly higher at 52.8 % and similar rates of 2.8 % each for local and distance recurrence. The higher re-excision rate was due to DCIS at the margins seen in 45 %. In the standard lumpectomy group, the completion rate to mastectomy was 17.1% due to inability to achieve clear margins after re-excisions. In contrast, none of the patients treated with oncoplastic reduction required completion to mastectomy. Conclusions: Large breasted patients with breast cancer treated with oncoplastic reduction had fewer surgeries due to decreased need for re-excision and completion mastectomies but similar local regional recurrence rates regardless of tumor characteristics.

P23

Dramatic Changes in Breast Cancer Grade Over the Past 36 Years J.D. Bishop,* A. Chagpar, M. Dixon, N.R. Horowitz, B. Killelea, T. Tsangaris, D.R. Lannin. *Yale University School of Medicine, New Haven, CT.*

Introduction: Since the widespread adoption of screening mammography in the US, the incidence of early stage breast cancers has increased dramatically, but the incidence of late stage cancers has not dropped proportionally. Recently it has been suggested that as many as 25% of currently diagnosed breast cancers may represent 'over-diagnosis', i.e. cancers that would have never bothered the patient within her lifetime. Changes in grade of breast cancer over time may be relevant to these hypotheses, but have not been studied carefully. Methods: Data on breast cancer from 1973 – 2009 was downloaded from the SEER 9 registry (November 2011 submission). In order to obtain population based incidence estimates, cases with missing data on grade were assumed to have the same distribution of grade as cases with known grade from the same year. Results: The proportion of grade 1 cancers has increased dramatically from 10.1% in the 1970s to 20.2% in the 2000s; during the same period of time, the proportion of grade 3 cancers has decreased from 65.2% to 38.0% ($p<0.001$). The figure shows that the overall increase in incidence of invasive cancer is due entirely to an increase in grade 1 and 2 cancers, whereas the incidence of grade 3 invasive cancer has declined by about 28%. ($p<0.001$) The increase in grade 1 and 2 tumors and decrease in grade 3 tumors is evident in women over 40 (change in cases/100,000 of +55, +89, and -71), but is not seen in women under 40 (+1, +3, and +1), suggesting that the changes are likely to be the consequence of screening mammography. The incidence of all 3 grades of in situ cancer has increased in women over 40 but not in women under 40. Conclusions: The overall increase in the incidence of invasive breast cancer is due to a dramatic increase in low grade cancers. The decreased incidence of high grade invasive cancers could be explained by treatment of increasing numbers of high grade DCIS, and this would be sufficient to explain the small reduction in breast cancer mortality from screening mammography. On the other hand, diagnosing and treating increasing numbers of low grade DCIS and invasive cancers may be of limited benefit and could reflect some over diagnosis.



P24

The Effect of Surgical Intervention and Ductal Carcinoma *In Situ* on the Durability of Pathologic Complete Response in Locally Advanced Breast Cancer Treated with Neoadjuvant Therapy: Does the Type of Surgery Affect Survival? A.T. Prescott,* H.M. King, T. Ambros, J.C. Villasboas, M.G. Moller, J. Hurley. *University of Miami, Jackson Memorial Hospital, Miami, FL.*

Introduction: In patients with locally advanced breast cancer (LABC) who achieve pathologic complete response (pCR), uncertainty exists over survival outcomes for those with residual Ductal Carcinoma in situ (DCIS). Centers with high breast conservation rates (57%-74%) show that residual DCIS in pCR predicts unfavorable outcomes. Recurrence rates in breast conservation surgery alone for DCIS approach 20%. We evaluated the impact of residual DCIS and type of surgery on the durability of pCR in a cohort of women with LABC. Methods: Retrospective review identified 808 patients with LABC who received neoadjuvant therapy at a tertiary referral center from 1991 to 2011. Patients were stratified by type of surgery and presence of DCIS in the surgical specimen. Log-rank test and Cox proportional hazards models were used to evaluate effect of residual DCIS and surgical modalities on progression free survival (PFS) and overall survival (OS). Results: 135 patients met inclusion criteria. Patients achieving pCR were 56% premenopausal, 64% Caucasian, 30% African-American, and 61% Hispanic. Clinical stage included: IIA (n=9, 7%), IIB (n=31, 24%), IIIA (n= 59, 45%), IIIB (n=28, 21%), and IIIC (n=5, 4%). Tumor receptors were ER negative (n=95, 71%), PR negative (n=75, 56%), and HER2 negative (n=71, 53%). Residual DCIS was present in 22 patients (16%); all underwent mastectomy. There were 113 patients (84%) that did not have residual DCIS; 94% of these patients had mastectomies. Overall mastectomy rate was 95%. Twelve patients with pCR (majority without DCIS) recurred with invasive disease and 6 patients (4%) died of other causes. Patients who achieved pCR with residual DCIS compared to those without DCIS had equivalent PFS and OS (p=0.5, p=0.6). Conclusion: In high risk patients with LABC who are predominantly treated with mastectomies, residual DCIS in pCR did not have a negative impact on progression free or overall survival. The survival benefit may be due to the use of mastectomy rather than breast conservation in pCR with residual DCIS.

P25

Pure Flat Epithelial Atypia (PFEA): Excise or Observe J.S. Berry,[1]* A.F. Trappey,[1] T. Vreeland,[1] G. Clifton,[2] A. Sears,[1] K. Clive,[1] S. Ferrise,[1] J.S. Saenger,[1] A.D. Kirkpatrick,[1] M. Lallemand,[3] G.E. Peoples.[1] *1. General Surgery, Brooke Army Medical Center, San Antonio, TX; 2. Blanchfield Army Community Hospital, Fort Campbell, KY; 3. Uniform Services University of the Health Sciences, Bethesda, MD.*

Background: PFEA on core needle biopsy (CNB) and the decision to proceed to excisional biopsy (EB) is controversial. We performed a retrospective review of our institutional experience with FEA to determine if a patient (pt) could be labeled low-risk, allowing for deferred EB in favor of radiologic follow-up. Methods: All surgical records were analyzed for women with a diagnosis of FEA from 2009 to 2012. CNB results were reviewed after processing via 3 H&E-stained step sections; if questions remained regarding the diagnosis, additional material was obtained using previously cut, unstained material. Pts with a separate surgical indication were excluded. The records of the remaining pts were reviewed for pt history, radiological, and pathological features including a previously agreed upon descriptor ("focal"(F)v"scattered/prominent"(SP)) of FEA. FFEA is defined as FEA involving 1 or a few adjacent acinar spaces, while SPFEA involves widespread acini or a larger confluent focus of FEA. The Fischer Exact Test was used to determine the significant differences between F and SP, termed nonfocal, groups while the Student-t test was used to compare means. Results: We evaluated 148 CNBs with FEA. PFEA was identified on 27 CNBs that were subsequently surgically excised. Final EB was benign in 24/27 cases (88%) and revealed associated DCIS in 3/27 cases(11%). No cases of invasive carcinoma were found. 18/27(67%) CNBs had a single focus of FEA while nine(33%) were described as nonfocal. 0/18 pts in the focal group had a malignancy on EB compared to 3/9 in the nonfocal group(0v33%, p=0.029). Of the 27 PFEA CNBs, 7 pts had a personal history of breast cancer (BrCa) whereas 20 did not. No malignancies were found in the 20 pts without a personal history of cancer versus 3 in pts with a history of BrCa(0/20v3/7,p=0.012). There were no differences in mammographic find-

ings, BIRADS classification, imaging guidance modality, gauge or number of biopsies, laterality of previous cancers, interval between CNB and surgical excision between groups. Conclusions: This data suggests it may be safe to defer EB and follow with short interval imaging in patients with PFEA which is focal and not associated with a personal history of BrCa.

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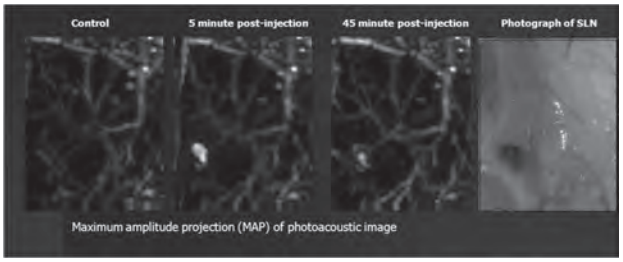
Recurrence Score Across the Age Spectrum: Is there an Age Discrimination? F. Smith,* M.C. Lee, G. Acs, W. Fulp, J. Lee, N. Khakpour, J.V. Kiluk, C. Laronga. *H Lee Moffit Cancer Center, Tampa, FL.*

Introduction: Treatment planning for early stage estrogen receptor (ER) positive, lymph node negative breast cancer was based on prognostic factors with limited predictive power such as age. The Recurrence Score (RS) from the Oncotype DX assay (ODX) provides predictive power transcending age but is rarely applied to the elderly or young patients (pts). We examined our experience with RS along the age continuum. Methods: Retrospective review was conducted of prospectively gathered breast cancer pts having a RS obtained as part of their cancer care. Eligibility for performance of the ODX was based on NCCN guidelines or physician discretion. Comparisons on RS were made by age groups (young: <45yrs; middle: >45yrs -<70yrs: elderly: >70yrs) using general linear regression model and the exact Wilcoxon Rank Sum Test. Results: 677pts had 681 tumors with RS available (89 young, 476 middle and 112 elderly pts). Median RS for the study pts was 17 (range 0-85) and 16, 17, and 15 for the young, middle, and elderly respectively. Median age was 58yrs (range: 27-95); young, middle, and elderly was 42, 58, and 74yrs respectively. Age as a continuous or categorical variable was not predictive of RS (p value = 0.38, 0.58 respectively). No significant differences were seen between age cohorts for histology, mitotic rate, lymphovascular invasion (LVI), grade, nodal status, stage, or strength of ER positivity. Mastectomy rates were higher in the young (57.5%), compared to the middle (42.5%) and elderly (39.6%) (p=0.02). Median invasive tumor size was 1.6, 1.5, and 1.5cm for young, middle and elderly. Larger tumor size, as a continuous variable, equaled higher RS (p=0.046). Other significant factors predicting higher RS were increased mitosis (p<0.001), LVI (p=0.013), high grade (p<0.001), and weak (<10%) ER positivity (p<0.001). Nodal status, stage, and histology did not affect RS. Conclusion: Age has limited predictive power for treatment planning for breast cancer. Age alone should not preclude recommendations for performance of ODX in estrogen receptor positive lymph node negative early stage breast cancer as the RS distribution across the spectrum of age is well matched.

P27

Optical Imaging of Axillary Sentinel Lymph Nodes with a Clinical Photoacoustic and Ultrasound System J.A. Margenthaler,* T.N. Erpelding, L.V. Wang. *Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

Introduction: Sentinel lymph node biopsy is the standard method of axillary staging for patients with clinically node-negative breast cancer. However, it requires an invasive surgical procedure for pathologic analysis with associated morbidity. In this pilot study, we have investigated the utility of a non-invasive photoacoustic and ultrasound sentinel lymph node identification system. Methods: Photoacoustic and ultrasound images of the axillary lymph nodes were collected before and after 0.1 mL intradermal injection of 1% methylene blue dye into the left forepaw pad of 7 healthy Sprague-Dawley rats using a photoacoustic imaging system adapted from a Philips iU22 clinical ultrasound. To investigate clinical translation, the imaging depth was extended up to 5 cm by adding chicken breast on top of the rat skin surface. 3D photoacoustic images were acquired by mechanically scanning the ultrasound transducer and light delivery fiber bundle along the elevational direction (Y axis). Co-registered images displayed photoacoustic signals using a pseudo-colormap ranging from blue to red over grayscale B-mode ultrasound images. Results: Pre-injection photoacoustic B-mode images featured photoacoustic signals from superficial blood vessels and skin surfaces. Five minutes post-injection, methylene blue accumulated in sentinel lymph nodes, as detected photoacoustically. When imaging depth was increased by adding biological tissue on top of the rat skin surface, lymph nodes were able to be identified at 5 cm depth. Optical spectra based on photoacoustic signals from sentinel lymph nodes closely matched the optical absorption spectrum of methylene blue, confirming the presence of methylene blue in detected lymph nodes (R = 0.995, Figure). Conclusion: Co-registered photoacoustic and ultrasonic images demonstrate the ability to combine functional (photoacoustic) and structural (ultrasonic) features for sentinel lymph node mapping. These results support the clinical investigation of photoacoustic and ultrasound imaging in the identification of sentinel lymph nodes with the potential for accurate, non-invasive staging of the axilla in breast cancer patients.



P28

High Tumor Grade Predicts Pathologic Complete Response in Breast Cancer Patients after Neoadjuvant Chemotherapy O.M. Fayanju,[1] Y. Yan,[1] D.B. Jeffe,[2] J.A. Margenthaler.[1]* *1. Department of Surgery, Washington University School of Medicine, St. Louis, MO; 2. Department of Medicine, Washington University School of Medicine, Saint Louis, MO.*

Introduction: Pathologic complete response (pCR) to neoadjuvant chemotherapy is associated with improved survival and lower rates of recurrence in breast cancer. We sought to identify factors associated with pCR. Methods: In a retrospective review of 5533 patients treated for breast cancer at our cancer center between 1999-2010, we identified patients with pathologically confirmed invasive breast cancer who received neoadjuvant chemotherapy. Clinical characteristics potentially associated with pCR were examined with chi-square tests and logistic regression. Stage, biomarker status, and factors significant at p<0.2 in univariate tests were included in multivariate logistic regression models. We report adjusted odds ratios (OR) and 95% confidence intervals (CI) significant at 2-tailed p<0.05. Results: Of the 879 patients who received neoadjuvant chemotherapy, 93 (10.6%) had pCR. In univariate tests, pCR was associated with younger age (p=0.01); pure ductal histology (p=0.0004); not receiving endocrine therapy &/or trastuzumab (p<0.0001); tumor grade 2 or 3 (p<0.0001); HER2 amplification (HER2+) (p<0.05); negative estrogen-receptor (ER-) and progesterone-receptor (PR-) status (both p<0.0001); and ER-/PR-/HER2+ status (p<0.01). In the multivariate model of individual biomarkers, HER2+ (OR 1.78, 95% CI 1.09-2.91) and grade 3 (OR 4.85, 95% CI 1.10-21.28) tumors predicted pCR. In the multivariate model of the composite biomarker ER-/PR-/HER2+, no lymph node involvement (OR 0.56, 95% CI 0.31-0.99), no trastuzumab therapy (OR 0.54, 95% CI 0.31-0.94), and grade 3 tumors (OR 5.23, 95% CI, 1.17-23.46) were predictive of pCR. In the model with the ER-/PR-/HER2- biomarker, only grade 3 tumors (OR 5.05, 95% CI 1.12-22.72) predicted pCR. Conclusion: Compared with grade 1 tumors, grade 3 tumors were 5 times as likely to result in pCR, regardless of biomarker status. The high mitotic activity of poorly differentiated tumors may make them more susceptible to the cytotoxic effects of chemotherapy. Further research is needed to determine whether pCR in association with grade 3 tumors results in improved breast cancer outcomes after neoadjuvant chemotherapy.

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Impact of Margin Assessment Method on Rate of Clear Margins at First Excision and Total Excision Volume T. Moo,[1]* L. Choi,[2] C. Olcese,[1] A. Heerdt,[1] L.M. Sclafani,[1] T.A. King,[1] A.S. Reiner,[1] S. Patil,[1] E. Brogi,[1] M. Morrow,[1] K.J. Van Zee.[1] *1. Memorial Sloan-Kettering Cancer Center, New York, NY; 2. Barbara Ann Karmanos Cancer Institute, Detroit, MI.*

Introduction The ideal method of margin assessment in breast conserving surgery (BCS) is unclear; options include Perpendicular (perpendicular margins in serial sections of the specimen), Tangential (pathologist-shaved margins from the specimen), and Cavity (surgeon-excised margins from the cavity). Which method most frequently achieves clear margins without increasing the volume of tissue excised is uncertain. We examined 3 different margin assessment methods as used by 6 experienced breast surgeons. Methods Patients undergoing BCS and sentinel node biopsy for breast carcinoma were identified from a prospective database. Patients undergoing surgery during July-

December for years in which each method was performed (Perpendicular 2003, Tangential 2004, Cavity 2011) were included. Multivariate analysis controlling for invasive tumor size and extensive intraductal component, and surgeon-specific analyses compared clear margins (no tumor at ink) at first excision and the total volume excised (including any re-excisions) to achieve clear margins (VOLUME) for each method. Results 562 patients were identified. Overall, the Tangential method had a significantly lower rate of clear margins at first excision than the Perpendicular and Cavity methods (52%, 86%, and 89% respectively; p<0.0001). 4 of 6 surgeons had the highest rates of clear margins on first excision with the Cavity method—significant when compared to the Tangential method but not the Perpendicular method (p=0.25). Comparison of the VOLUME among the 3 methods was variable by surgeon. 3 surgeons showed no significant difference in volume among the different methods, while 3 had significantly higher volumes with Cavity compared to Perpendicular. Conclusions Overall, Cavity and Perpendicular were similar in achieving clear margins at first excision with a trend toward higher clear margin rate with the Cavity method. The effect of method on VOLUME varied among surgeons. While the Cavity method may improve rates of clear margins on first excision, its effect on VOLUME is variable among surgeons and may result in an increase in the total volume excised.

Table. Comparison of 3 different methods of margin assessment in 6 surgeons: rate of clear margins at first excision and total volume excised to achieve clear margins, by surgeon.

		Cavity Shave (n=291)		Perpendicular (n=145)		Tangential (n=126)	
	N	Clear margins on first excision	Total volume in cc to clear margins, median (range)	Clear margins on first excision	Total volume in cc to clear margins, median (range)	Clear margins on first excision	Total volume in cc to clear margins, median (range)
Surgeon A	139	86%	73.6 (11.7-488.8)	92%	86.8 (21.2-394.1)	45%	106.2 (10.8-277.6)
Surgeon B	53	94%	33.8 (10.2-130.1)	75%	52.8 (7.3-179.8)	50%	50.3 (15.7-101.2)
Surgeon C	164	82%	50.6 (4.3-209.0)	83%	31.8 (6.9-121.4)	34%	32.2 (5.4-173.6)
Surgeon D	52	91%	113.7 (23.6-239.3)	63%	102.7 (25.1-265.9)	70%	83.9 (28.0-282.0)
Surgeon E	80	97%	86.3 (9.5-612.3)	88%	62.8 (9.0-158.9)	70%	74.9 (32.3-203.5)
Surgeon F	74	92%	88.1 (8.3-657.3)	89%	51.1 (12.5-202.9)	63%	82.7 (22.4-215.9)
Total	562	89%	62.0 (4.3-657.3)	86%	55.3 (6.9-394.1)	52%	63.9 (5.4-282.0)

cc, cubic centimeters

P30

Patient-Reported Satisfaction after Contralateral Prophylactic Mastectomy and Implant Reconstruction L.A. Pharmer,* S.B. Koslow, A.M. Scott, M. Stempel, M. Morrow, A.L. Pusic, T.A. King. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Rates of contralateral prophylactic mastectomy (CPM) have increased despite the lack of survival benefit. Using the BREAST-Q, a validated condition-specific patient-reported outcome instrument which measures breast surgery-related patient satisfaction and health-related quality of life (HR-QoL), we sought to determine whether satisfaction and HR-QoL differ between patients with implant reconstruction (IR) +/- CPM. Methods: From 2000-07, 3,874 patients with stage 0-III primary unilateral breast cancer had mastectomy, and 688 (18%) had CPM w/in 1 year. Prospectively collected BREAST-Q data was available for 294 (8%) patients. The BREAST-Q Reconstruction module consists of independent scales (scores 0-100) that evaluate 5 domains: Satisfaction with Breasts, Satisfaction with Outcome, Psychosocial, Sexual, and Physical well-being. Univariate analysis and multivariate models (MVA) were used to assess satisfaction and HR-QoL in pts with IR +/- CPM. Results: Of 294 pts with BREAST-Q data, 112 (38%) had CPM. Patients completing the BREAST-Q did not differ from those who did not. CPM patients were younger (mean 47 v 50 yrs; P=0.001), more likely to be Caucasian (98% v 86%; P=0.001), and to have a family history of breast cancer (60% v 44%; P=0.011). Median time from mastectomy +/- CPM to BREAST-Q was 52 mos and did not differ between groups. There was no difference in stage, adjuvant treatment, overall complications, or recurrences between groups at the time of BREAST-Q survey. Pts with CPM had a higher mean score for Satisfaction with Breasts (64 v 55, P<0.001) and Satisfaction with Outcome (75 v 68, P=0.007); other HR-QoL domains did not differ. On MVA (table) CPM and the absence of lymphedema were significant predictors of Satisfaction with Breasts (CPM P= 0.005, lymphedema P=0.034). CPM was not associated with improved Satisfaction with Outcome. Conclusion: A growing number of breast cancer patients pursue CPM; hence, understanding how CPM may impact long term satisfaction and HR-QoL is essential. This study suggests that, in the setting of IR, CPM positively correlates with Satisfaction with Breasts, but not with improvements in other HR-QoL domains.

Table. Multivariate analyses for predictors of Satisfaction with Breasts and Satisfaction with Outcome

	Satisfaction with Breasts			*Satisfaction with Outcome*		
Variable	Δ in BreastQ score (β)	95% CI	*P* value	Δ in BreastQ score (β)	95% CI	*P*
CPM	6.7	2.0, 11.4	0.005*	4.6	-0.9, 10.0	0.099
Caucasian	6.7	-1.3, 14.6	0.099	-0.9	-10.1, 8.4	0.855
Postmenopausal	-3.6	-8.3, 1.0	0.122	-4.7	-10, 0.7	0.089
Married	1.0	-4.4, 6.4	0.714	1.0	-5.3, 7.2	0.765
FH of breast cancer	-2.6	-6.9, 1.8	0.248	-0.9	-5.9, 4.2	0.733
Invasive cancer vs DCIS	-5.2	-10.8, 0.5	0.072	-4.3	-10.9, 2.2	0.196
Multifocal/multicentric	-4.2	-8.6, 0.1	0.057	-0.7	-5.8, 4.3	0.776
ALND	-2.9	-8.8, 2.9	0.326	-1.2	-8.0, 5.6	0.736
Silicone vs saline	3.3	-1.2, 7.8	0.149	2.6	-2.6, 7.8	0.324
Nipple reconstruction	1.5	-3.3, 6.2	0.546	7.8	2.3, 13.3	0.006*
Radiation	0.6	-6.4, 7.6	0.860	3.2	-4.9, 11.4	0.427
Capsular contracture	-3.0	-8.0, 2.0	0.239	-1.4	-7.3, 4.4	0.625
Lymphedema	-8.7	-16.8, -0.7	0.034*	-9.9	-19.2, -0.5	0.039*
Months post-surgery	0.1	-0.1, 0.2	0.405	0.1	-0.1, 0.2	0.548

Dependent Variable: Satisfaction with Breasts: R^2=0.150, Satisfaction with Outcome: R^2=0.093; CPM, contralateral prophylactic mastectomy; FH, family history; DCIS, ductal carcinoma in situ; ALND, axillary lymph node dissection; Δ change; *statistically significant P-value; β, beta-coefficient; CI, confidence interval.

Table. Multivariate analyses for predictors of Satisfaction with Breasts and Satisfaction with Outcome

P31

A Prospective Trial of a Directed Home Exercise Program (HEP) for Weight Maintenance in Breast Cancer Patients E. Orell,* S. Kramer, S. Patil, D. Wilson, E. Williams, M. Morrow, A. Heerdt. *MSKCC, New York, NY.*

Introduction: Weight gain is a common side effect of chemotherapy for breast cancer and is associated with a poorer prognosis. While exercise theoretically should improve weight maintenance, studies are not consistent and the most effective exercise program is unclear. We investigated the viability of utilizing a directed HEP for weight maintenance during treatment. Methods: With IRB approval, women undergoing chemotherapy after breast cancer surgery from 5/10-3/12 were asked to participate in a HEP, which included 3 modules; stretches, sequential movements for body alignment, walking and weight training. A trained instructor initially demonstrated the modules and contacted patients weekly for support. Body fat analysis, body mass index (BMI), and weight measurements were performed at baseline, the end of chemotherapy, the end of radiotherapy (when indicated), and at one year follow up. Statistical analysis was performed with SAS. Results: 90 patients were accrued and complete data at one year follow up was available for 57. The mean age was 51 (range 25-72). 42% were post-menopausal, 58% had breast conservation therapy, and 34% had axillary lymph node dissection. 84% were compliant with the exercise program overall, exercising on average 4.7 times per week. Increased compliance was seen in patients with weight gain or loss less than 6 months prior to treatment. There was a statistically significant decrease in percentage body fat from baseline to the end of chemotherapy (p=0.02) present in all groups, but significantly greater in the post-menopausal group (p=0.0042). Weight, BMI, and percentage body fat parameters and p-values are presented in the table. Conclusion: Overall, patients were compliant with the HEP and had a decrease in weight, BMI, and percentage body fat. This program appears to be effective in achieving weight maintenance in a breast cancer population using minimal resources, making it suitable for use in a wide variety of settings.

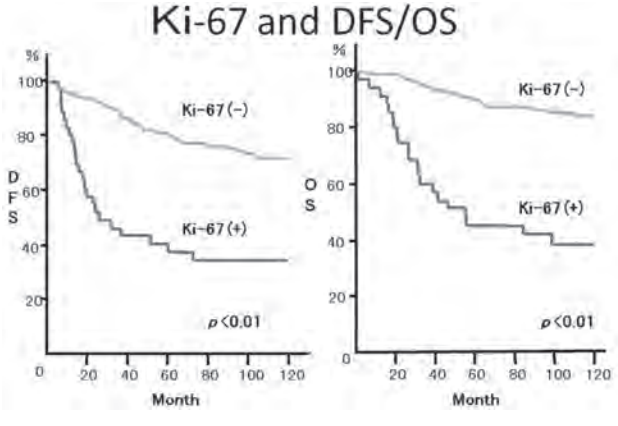
	Weight (kg)	BMI	% Body Fat
Baseline	69.72	26.95	34.09
End of chemotherapy	68.66 (p=0.50)	26.18 (p=0.15)	32.41 (p=0.02)*
One year follow up	67.58 (p=0.90)	25.79 (p=0.48)	33.14 (p=0.27)

Table. Mean weight (kg), body mass index, and percentage body fat parameters and p-values in patients at baseline, the end of chemotherapy, and at one year follow up. P-values are compared to baseline.

P32

Great Potential of Ki-67 as a Predictive Prognostic Biomarker in Resected Localized Breast Cancer with No Prior Treatment who were Followed up for 10 Years H. Nishimiya,* K. Yamashita, Y. Kosaka, M. Kikuchi, H. Katoh, T. Enomoto, N. Sengoku, M. Kuranami, M. Watanabe. *Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan.*

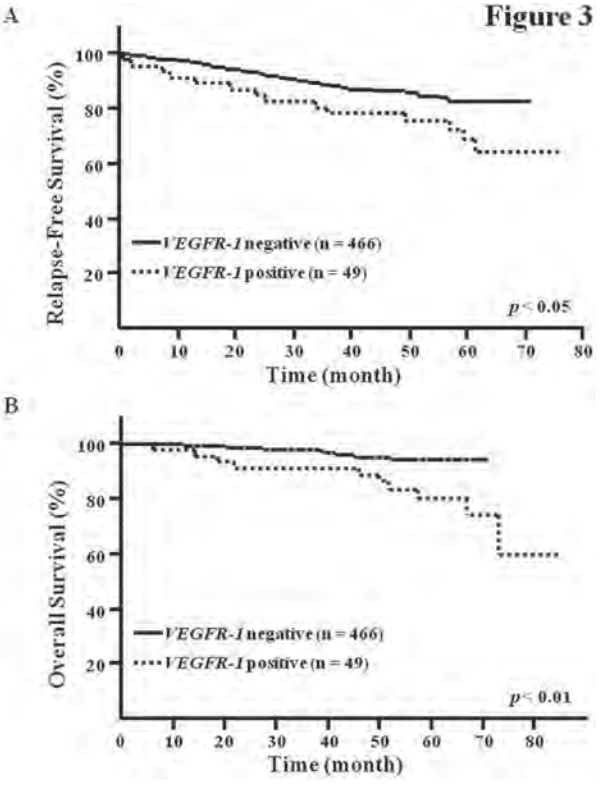
(Background) In order to know accurate survival outcome of breast cancer, 10 years follow-up is required and such long-term survival information remains few. (Patients and Methods) We recruited 253 breast cancer patients who undertook operations between 1995 and 1999. Ten-year OS/DFS were evaluated by clinical factors including preoperative tumor markers, pathological factors and tumor biological characters (Ki-67, HER2, ER, and PR). Prognosis was compared by a long-rank test and multivariate proportional hazard model was applied to the significant predictors (P<0.05). (Results) The 253 patients were composed of 84/112/57 in Stage I/II/III, respectively, who included 62 tumor deaths (24.5%). The significant univariate prognostic factors were T factor, N factor, preoperative CEA (preCEA), ER, PR, HER2, and Ki-67. T factor, preCEA, ER, PR, and Ki-67 were independent prognostic factors by multivariate analysis. Ki-67 could be an excellent prognostic factor in each stage (P<0.01). The luminal A group showed the best survival outcomes in chemo-naive breast cancer patients. On the other hand, HER2 positive or triple negative (TN) groups showed worse prognosis than the luminal A, and Ki-67 showed potent prognostic relevance in such aggressive subgroups (P<0.01). The multivariate sub-analysis again revealed that Ki-67 could be an independent prognostic factor even in aggressive breast cancer such as HER2 positive or TN groups. (Conclusion) Ki-67 has a great potential of prognostic biomarker in aggressive breast cancer, and such prognostic information could be beneficial for development of novel therapeutic strategy.



P33

Vascular Endothelial Growth Factor Receptor-1 mRNA Overexpression in Peripheral Blood as a Useful Prognostic Marker in Breast Cancer Y. Kosaka,[1]* A. Kataoka,[3] H. Yamaguchi,[3] N. Sengoku,[1] M. Kuranami,[1] S. Ohno,[3] M. Watanabe,[1] K. Mimori,[2] M. Mori.[2] *1. Kitasato University School of Medicine, Kanagawa, Japan; 2. Medical Institute of Bioregulation, Kyushu University, Oita, Japan; 3. Kyushu Cancer Center, Fukuoka, Japan.*

Introduction: Identification of useful markers associated with poor prognosis in breast cancer patients is critically needed. We previously showed that expression of vascular endothelial growth factor receptor-1 mRNA in peripheral blood may be useful to predict distant metastasis in gastric cancer patients. However, expression of vascular endothelial growth factor receptor-1 mRNA in peripheral blood of breast cancer patients has not yet been studied. Methods: Real-time reverse transcriptase-PCR was used to analyze vascular endothelial growth factor receptor-1 mRNA expression status with respect to various clinical parameters in 515 patients with breast cancer and 25 controls. Results: Expression of vascular endothelial growth factor receptor-1 mRNA in peripheral blood was higher in breast cancer patients than in controls. Increased vascular endothelial growth factor receptor-1 mRNA expression was associated with large tumor size, lymph node metastasis, and clinical stage. Patients with high vascular endothelial growth factor receptor-1 mRNA expression also experienced a poorer survival rate than those with low expression levels, including those patients with triple-negative type and luminal-HER2(-) type disease. Conclusions: Expression of vascular endothelial growth factor receptor-1 mRNA in peripheral blood may be useful for prediction of poor prognosis in breast cancer, especially in patients with triple-negative type and luminal-HER2(-) type disease.



P34

A Negative Axillary Ultrasound Can Exclude Advanced Nodal Disease in Breast Cancer Patients L. Van Roozendaal,[1] R. Schipper,[1]* B. De Vries,[3] R. Beets-Tan,[2] M. Lobbes,[2] 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 Pathology, Maastricht, Netherlands.*

Background: After the ACOSOG-Z0011 trial, preoperative differentiation between no or limited (pN0-pN1) and advanced axillary nodal disease (pN2-pN3) becomes more relevant in order to prevent completion axillary lymph node dissection (ALND) in breast cancer patients with limited nodal disease and to prevent omitting ALND's in patients with advanced nodal disease. The aim of this study was to determine whether an axillary ultrasound could differentiate between no or limited and advanced axillary disease. Materials and Methods Between January 2008 and March 2012, all consecutive patients with operable primary invasive breast cancer were included. Patients treated with neo-adjuvant therapy were excluded. Data concerning sex, age, diagnostic

work-up, surgical procedures and histopathological findings were retrospectively collected. False negative findings and negative predictive values for axillary nodal staging with ultrasound were calculated. Results A total of 564 consecutive patients were included, resulting in 577 axillary ultrasounds (bilateral breast cancer in 13 patients). After a negative ultrasound, pathology showed pN2-pN3 disease in 4.4% of the patients. If a cN1 was predicted, pathology showed pN2-pN3 disease in 41.2% of the patients. Nodal tumor load was significantly less in patients with cN0 but postoperative pN1, compared to cN1 with postoperative pN1 (1.4 vs. 2.0 positive lymph nodes ($p<0.01$)). Conclusion In conclusion, a negative ultrasound in primary breast cancer patients excludes advanced nodal disease and consequently selects patients with no or favorable pN1. It cannot differentiate between limited and advanced nodal disease. Therefore, after a negative ultrasound the Z11 design can be implemented in daily practice.

Clinical nodal status of all axillae with corresponding final nodal and tumor size status.

		pN0	pN0i+	pN1mi	pN1	pN2	pN3	Total
cN0								
	T1	269	8	22	30	5	1	365
	T2	74	13	14	23	8	3	135
	T3	3	4	1	6	2	3	19
	T4	1	-	-	1	1	-	3
	total	347	55	37	60	16	7	522
cN1								
	T1	-	-	-	9	1	4	14
	T2	-	-	-	18	7	5	30
	T3	-	-	-	4	2	3	9
	T4	-	-	-	-	-	-	0
	total	0	0	0	31	10	12	53
cN2								
	T1	-	-	-	-	-	-	0
	T2	-	-	-	-	-	1	1
	T3	-	-	-	-	1	-	1
	T4	-	-	-	-	-	-	0
	Total	0	0	0	0	1	1	2
Total		347	55	37	91	27	20	577

P35

Short-Term Sequela of Intraoperative Radiation after Breast Conserving Surgery R.N. Goble,* J. Drukteinis, M. Lee, N. Khakpour, J.V. Kiluk, C. Laronga. *Moffitt Cancer Center, Tampa, FL.*

Background: Intraoperative radiation therapy (IORT) is an emerging option for partial breast radiotherapy in select women with early breast cancer. Our objective was to assess short-term clinical and sonographic findings after breast conservation (BCT) and IORT. Methods: An IRB-approved, single institution retrospective chart review was conducted of patients (pts) treated with BCT/IORT from 1/2011- 6/2012. Follow-up clinical breast exams and ultrasounds (US) obtained 6 and 12months after BCT/IORT were retrospectively reviewed by a breast radiologist (JD) for sonographic findings (Table 1). P-values were calculated using McNemar's test, Wilcoxon Rank Sum Test, and Chi-square. Results: 71pts underwent BCT/IORT. Mean age was 71.6 yrs (range 54-88). Of 71pts, 10 (14%) / 5 (7%) pts were symptomatic at 6/12month follow-up respectively. Eleven pts had deep tissue closure (DTC) of the lumpectomy cavity with 5/11 (45%) DTC pts being symptomatic at follow-up vs. 5/60 (8%) without DTC. 38/71 (54%) pts had at least one US; 35pts had 6month US (22 without a 12month US) and 16pts had a 12month US (3 without a 6month US). All 38pts had a seroma but, 10/38 (26%) pts were symptomatic. At 6months, 9/35 (26%) pts had a symptomatic seroma [7 (78%) with pain and 2 (22%) with overlying skin hyperemia]. Two pts required seroma aspirations at 6months; 1 had repeat aspiration at 12months. At 1-year follow-up, 4/9 (44%) pts had persistent symptoms. One asymptomatic pt at 6months reported pain at 1 year despite no change in seroma appearance [total 5/16 (31%)]. At 6 months, DTC resulted in smaller seroma cavity volumes compared to those without closure ($p = 0.03$). However there was no difference in cavity resorption between the two groups over time ($p = 0.67$) and no significant change in seroma volume or wall thickness for either group. There was no difference in sonographic findings between the two groups at 6/12months. Conclusion: Presence of a seroma is commonplace post BCT/IORT; symptomatic seromas are uncommon. DTC generated smaller but more symptomatic seromas. Longer follow-up with serial US performed in all BCT/IORT pts is advisable to document natural progression of symptoms and seromas.

Sonographic Findings after Breast Conserving Surgery and Intraoperative Radiation

	6mo US n=35	12mo US n=16
Seroma size (mean)	24.1x15.6x18.8mm	20.6x11.3x18.8mm
Seroma wall thickness (mean)	3.02mm	2.16mm
Seroma volume (mean)	8.27cc	9.21cc
Symptomatic	9 (26%)	5 (31%)
Complex seroma with adherent hyperechoic debris	12 (34%)	5 (31%)
Hematoma	4 (11%)	0 (0%)
Thin septations	14 (40%)	8 (50%)
Thick septations	8 (23%)	2 (13%)
Simple seroma	9 (26%)	4 (25%)
Low level internal echoes	9 (26%)	3 (19%)
Deep tissue closure (DTC)	10	6
DTC seroma size (mean)	19.9x10.6x15.0mm	17.8x8.5x16.3mm
DTC seroma wall thickness (mean)	4.8mm	2.3mm
DTC seroma volume (mean)	5.74cc	6.86cc

P36

Reoperation after Breast Conservation in the United States R.J. Bleicher,[1]* K. Ruth,[2] E.R. Sigurdson,[1] M. Boraas,[1] B. Egleston.[2]
1. Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA;
2. Biostatistics, Fox Chase Cancer Center, Philadelphia, PA.

Introduction: Breast conservation surgery (BCS) is standard treatment for breast cancer, but reexcision and completion mastectomy trends in the United States remain unknown. This study was performed to delineate those trends and their predictors in Medicare patients. Methods: SEER data linked to Medicare claims were reviewed for BCS patients having nonmetastatic invasive breast cancer between 1992 and 2005. Patients underwent BCS with nodal evaluation as their first therapeutic procedure. Results: Among 33,197 patients first having BCS, 5,143 patients (15.5%) underwent reoperation, with 2,039 (39.6%) having mastectomy. Between 1992 and 2005, reoperation rose from 8.8 to 18.5%: patients having reexcision(s) but no mastectomy increased from 4.8 to 11.8% ($p<0.0001$) while patients proceeding to mastectomy increased from 4.0 to 6.7% ($p<0.0001$). Image-guided localization use at 1st BCS increased from 6.4 to 51.0% of patients ($p<0.0001$). Mean tumor size in those not having reexcision, having reexcision but not mastectomy, and having mastectomy, were 1.52, 1.62, and 2.16 cm, respectively ($p<0.0001$) with no change over time in the latter two groups ($p=0.48$, and 0.21, respectively). Predictors of reoperation included age, diagnosis year, urban/rural setting, tumor size, grade, histology, preoperative excisional biopsy, and image-guided localization use (all $p<0.0001$), and race ($p=0.05$). Gender, ER/PR status, mammogram, ultrasound, and breast MRI use were not predictive. Predictors of BCS conversion to mastectomy included age, diagnosis year, tumor size, grade, histology (all $p<0.0001$), ER/PR status ($p=0.0003$), preoperative excisional biopsy ($p<0.0003$), mammogram use ($p=0.017$), and image-guided localization at surgery ($p=0.02$). Race, urban/rural setting, number of reexcisions, ultrasound, and breast MRI use were not predictive. Conclusions: Reoperation after BCS, despite stable tumor sizes and increasing localization use, has more than doubled. This has major resource, cost, and morbidity implications, and efforts to address this trend are needed. Unified recommendations for reoperation, based on outcomes, are needed and should be a high priority for the surgical oncology community.

P37

Impact of Bilateral versus Unilateral Mastectomy on Short Term Outcome and Adjuvant Therapy T. Czechura,* D.J. Winchester, C. Pesce, E. Barrera, D.P. Winchester, K. Yao. *NorthShore University HealthSystem, Evanston, IL.*

Background: Bilateral mastectomy (BM) has become an increasingly more common treatment choice for women with breast cancer but the impact on length of stay (LOS), readmission rate, 30-day mortality, and delay of adjuvant therapy is unknown. We hypothesized that relative to unilateral mastectomy (UM), BM may significantly impact these factors. Methods: Using the National Cancer Data Base, we selected non-neoadjuvant Stage 0-III breast cancer patients who underwent either UM or BM from 2003-2010 with and without reconstruction. We used chi-square and logistic regression models for the analysis. Results: Of 390,712 patients treated with mastectomy, 315,278 (81%) had UM and 75,437 (19%) had BM. 97,031 (25%) underwent reconstruction; 58,985 (19%) UM had reconstruction versus 38,046 (50%) for BM. The median number of days to discharge for the entire cohort was 1.0 (range 0-184) in the UM group versus 2.0 (range 0-182) in the BM group ($p<0.001$).

Adjusting for UM vs. BM, breast reconstruction, age, race, insurance status, stage, co-morbidities, facility type and location, BM patients were more likely (OR=1.41 95%CI: 1.37-1.44) to have a longer hospital stay than UM patients. Thirty day mortality and readmission rates to the hospital were not significantly different between BM and UM. The median number of days from diagnosis to definitive surgery, chemotherapy, hormonal therapy, and radiation therapy was statistically longer in the BM group compared to the UM group (Table I). After adjusting for the aforementioned factors, these differences persisted for definitive surgery (OR= 1.2 95% CI: 1.19-1.24), hormonal treatment (OR=1.10 95% CI: 1.05-1.12), radiation therapy (OR=1.06 95% CI: 1.02-1.11), and chemotherapy (OR=1.12 95% CI: 1.09-1.15). Similar findings persisted when limiting the analysis to women without reconstruction. Conclusions: Delays in adjuvant treatment and LOS are statistically longer for BM irrespective of reconstruction, but these delays are not clinically significant. The selection of a unilateral or bilateral operation does not lead to critical differences in short term outcomes and timely delivery of care.

Table I. Days from Date of Diagnosis to Specific Treatments in the Entire Cohort, 2003-2010

Date of Diagnosis to:	UM	BM	p-value
Definitive Surgery	33 days	40 days	<0.001
Chemotherapy	66 days	69 days	<0.001
Hormonal Therapy	136 days	170 days	<0.001
Radiation Therapy	210 days	215 days	<0.001

P38

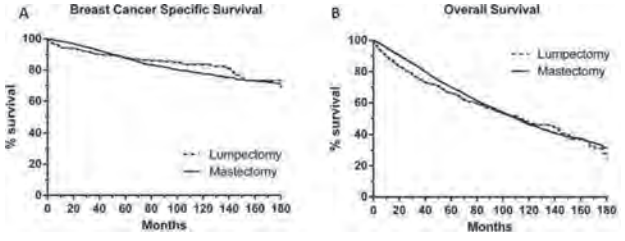
Accurate Staging with Internal Mammary Chain Sentinel Node Biopsy for Breast Cancer J.L. Gnerlich,[1]* J. Barreto-Andrade,[1] T. Czechura,[2] M. Turk,[2] D.J. Winchester.[2] *1. University of Chicago Medical Center, Chicago, IL; 2. NorthShore University HealthSystem, Evanston, IL.*

Background: Although up to one third of breast cancer patients have lymphatic drainage to their internal mammary chain, harvesting IMC sentinel nodes (IMC-SN) remains controversial. We sought to determine predictors for IMC nodal positivity and the role positive IMC-SNs have on changing prognosis and management. Methods: We reviewed a prospectively collected database to identify patients who had IMC drainage detected on lymphoscintigraphy and underwent IMC-SN biopsy. Lymphoscintigraphy was performed following peritumoral (87%) or periareolar (13%) injection of technetium-labeled sulfur colloid. Chi-square tests and logistic regression models were used to determine trends and factors associated with IMC node positivity. Results: Between 1997 and 2012, IMC-SN biopsy was performed in 123 patients without any complications. The mean age of the cohort was 53 years and mean tumor size was 2.0cm. Sentinel nodes mapped to only the IMC in 14 (11%) of patients. Mean number of IM nodes removed was 1.6. The 2nd intercostal space (ICS) was the most sampled (53%) followed by the 4th ICS (22%). Primary tumor location was as follows: UIQ (32%), UOQ (28%), LIQ (23%), LOQ (11%), and central (6%). Overall, 26% of patients were node positive with 12 patients (10%) having positive IMC-SNs. Of the positive IMC-SN biopsies, a majority of patients (83%) also had positive axillary SNs, whereas 2 patients (17%) had IMC-SN as their only positive node. In patients with a positive axilla, IMC-SN was also positive in 33% of patients. In patients with a negative axilla, IMC-SN was positive in 2.5% of cases (p<0.001). Number of positive axillary nodes was the only independent predictor of IMC positivity (1-3 + axillary nodes OR: 14.4, 95% CI: 2.7-78.1; >4 + axillary nodes OR: 38.5, 95% CI: 3.5 - 429.0). IMC-SN positivity led to a more advanced N category in 10% of patients and to upstaging in 4 (33%) patients. Conclusions: IMC-SN biopsy can be safely performed. One third of patients with positive axillary SNs also had a positive IMC-SN suggesting that IMC metastases are not rare. When identified, IMC-SN biopsy has the potential to alter the stage and adjuvant therapy of breast cancer patients.

P39

Increasing Use of Lumpectomy in Men with Breast Cancer: Outcomes Analysis of SEER Data 1983-2009 J.M. Cloyd,* I.L. Wapnir. *Stanford University, Stanford, CA.*

Introduction: Although mastectomy is considered the gold standard in male breast cancer (MBC), the utilization of lumpectomy and its impact on outcomes in MBC patients has not been previously studied. Methods: The Surveillance, Epidemiology and End Results (SEER) database was used to identify all MBC patients who underwent either mastectomy or less than mastectomy (ie lumpectomy) between 1983 and 2009. Differences between treatment groups were assessed via Chi Square test. Influence of surgery type on breast cancer specific survival (BCSS) and overall survival (OS) were analyzed. Results: 4707 (86.8%) men underwent mastectomy while 718 (13.2%) underwent lumpectomy. A greater proportion of patients underwent lumpectomy later in the study period (1983-1986, 10.6% vs 2007-2009, 15.1%). A greater percentage of lumpectomy patients were 80 years or older (21.3% vs 16.3%), had Stage IV or unknown stage disease (28.7% vs 15.3%) and had no nodal sampling (34.3% vs 6.9%). Only 35.4% of patients underwent adjuvant radiation therapy following lumpectomy, compared to 20.8% of mastectomy patients. Factors predictive of a patient receiving lumpectomy on multivariate logistic regression included age ≥80 (OR 1.3, 95% CI 1.0-1.7), black race (OR 1.3, 95% CI 1.0-1.6), and Stage IV disease (OR 1.6, 95% CI 1.1-2.2). Kaplan-Meier analysis demonstrated no difference in unadjusted BCSS but lower OS for patients undergoing lumpectomy (Figure). On logistic regression, lumpectomy was not independently associated with worse BCSS (OR 0.81, 95% CI 0.59-1.10) or OS (OR 0.76, 95% CI 0.62-0.94) after controlling for age, race, stage, grade and whether radiation was received. Conclusions: Lumpectomy is performed in a small, but growing, proportion of MBC patients. These patients are not only older and more likely to have advanced disease at the time of diagnosis, but also are less likely to receive standard of care therapy such as lymph node sampling and adjuvant radiation. These findings suggest that surgeons may be utilizing lumpectomy for palliative rather than breast conserving purposes. Despite these observations, breast cancer specific survival is unaffected by the type of surgery.



P40

Upstaging of Atypical Ductal Hyperplasia and Flat Epithelial Atypia to Ductal Carcinoma *In Situ* and Invasive Breast Cancer M. Lazar,[1]* C. Gresik,[1] M. Sullivan,[2] I. Helenowski,[2] S. Khan,[1] K.P. Bethke,[1] J.S. Jeruss,[1] N.M. Hansen.[1] *1. Breast Surgery, Lynn Sage Comprehensive Breast Center at Northwestern Memorial Hospital, Chicago, IL; 2. Northwestern University, Chicago, IL.*

Purpose: At present, surgical excision is recommended for most patients following a core needle biopsy (CNB) diagnosis of FEA and ADH. To evaluate the need for excision of these lesions, we assessed the risk of upstaging to DCIS or invasive carcinoma following a diagnosis of FEA or ADH on CNB. Methods: Following IRB approval, we queried our pathology database for all patients who were diagnosed with FEA or ADH on CNB and had a subsequent excision from 2003 to 2010. Records were reviewed to obtain imaging, operative, and pathology reports. Women whose CNB showed DCIS or invasive cancer associated with FEA or ADH were excluded, as were women who had prior breast and/or chest wall radiation, or a history of breast cancer. The CNB procedures were performed using ultrasound, stereotacatic, and MRI guidance. Core needles ranged from 9 to 14 gauge. Since we converted to digital imaging in 2007, we analyzed rates separately from 2003-2006 (inclusive) and 2007-2010 (inclusive). Results: We identified 249 women (mean age 57.2), 170 women with pure ADH (mean age 57.6) and 79 women with FEA (mean age 56.2). In the ADH group, 18 (10.6%) were upstaged at surgical excision (14 had DCIS, 8.2% and 4 had invasive cancer, 2.4%) and in the FEA group, 4 women (5.1%) were upstaged at surgical excision (3 had DCIS, 3.8% and 1 had invasive cancer, 1.3%). From 2003-2006, 4 women were upstaged from ADH to invasive cancer, compared to 0 from 2007-2010 (P=0.098). From 2003-2006, 9 women were upstaged from ADH to DCIS, compared to 5 women upstaged to DCIS from 2007-2010 (P=0.73). We were unable to determine any radiologic finding (calcifications, mass) associated with upstaging. Conclusion: The frequency of upgrades from ADH to DCIS or invasive cancer over a recent time period is lower in our experience (10.6%) than previous reports (20-25%); it is also lower for FEA (5.1%) than for ADH. There was a non-significant trend for lower

upstaging following conversion to digital mammography. These data suggest that routine excision of all FEA is not necessary, and that of ADH needs investigation to identify women with an extremely low risk of upstaging.

P41

Post Mastectomy Radiation for Stage ll Breast Cancer Patients with T1/T2 Lesions S. Libson,[1]* H.M. King,[1] C. Ma,[1] P. Eduardo,[1] C. Takita,[2] E. Avisar.[1] *1. Department of Surgery, Miller School of Medicine, Miami, FL; 2. Department of Radiation Oncology, Miller School of Medicine, Miami, FL.*

Background: Post mastectomy radiation (PMR) is usually recommended for T3 or N2 breast cancer (BC). The role of PMR for stage ll BC with T1/T2 lesions remains controversial. The aim of this study was to assess the role of PMR in this subgroup of patients. Methods: A retrospective analysis of a prospectively collected database of all stage ll BC patients treated with mastectomy at our institution between 2005-2008 was performed. Demographics, pathology, failure patterns and disease free survival rates were compared between the patients who received PMR vs. those who were not radiated (NR). Results: Eighty two patients underwent mastectomies for stage II disease with a T1/T2 lesion. Twenty two of those (27%) received PMR. The median follow up time was 47 months. The patients in the PMR group had larger tumors (90% vs. 64%) and higher grade histology (59% vs. 32%). Three patients in the NR group had a distant recurrence compared to 2 patients in the PMR group. No difference was found in term of DFS between the 2 groups. Four patients had a chest wall recurrence (CWR) in the (NR) group compared to none in the PMR group; however this was not statistically significant. A Kaplan Meier analysis of time to CWR in the NR group was performed. Mean time to CWR was 78.9 months. The time to CWR was significantly lower in the ER negative group compared to the ER positive group (64 vs. 82 months, p=0.029). CWR free rate at 5 years was 100% in low grade tumors vs. 53% in high grade tumors, (p=0.001). All CWR occurred in the node negative group, (p=0.003). In terms of treatment variables only hormonal treatment was found significant with a mean time to recurrence of 64.9 months in the non hormonal treated group vs. 82.3 months in the hormonal treated group, (p=0.038). In a Cox regression multivariate analysis none of those factors maintained significance. Conclusion: ER negative status, high grade and node negativity were associated with CWR in post mastectomy stage ll BC with T1/T2 lesions. A prospective trial randomizing stage II BC patients with T1/T2 lesions, negative hormone receptors and high grade tumors to PMR following mastectomy vs. NR is recommended.

P42

IL-6 as a Biomarker for Lymphedema E. Weitman,[1]* J. Zampell,[1] S. Aschen,[1] G. Farias-Eisner,[1] D. Cuzzone,[1] S. Ghanta,[1] N. Albano,[1] S. Rockson,[2] B.J. Mehrara.[1] *1. Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; 2. Stanford University, Stanford, CA.*

Background: Lymphedema is a common complication of cancer treatment; however, current diagnostic options are limited and rely primarily on limb circumference or volume measurements. Identification of a serum marker for lymphedema may facilitate diagnosis and response to treatment. Lymphedema is characterized clinically by adipose tissue deposition and inflammation; therefore, we investigated serum and tissue levels of interleukin-6 (IL-6), an important physiologic regulator of these processes. Methods: We used a variety of mouse models to test the hypothesis that lymphatic fluid stasis increases the expression of IL-6, including microsurgical disruption of the superficial and deep lymphatics of the tail and axillary lymph node dissection (ALND). In order to translate our findings clinically, we analyzed IL-6 expression in serum samples obtained from breast cancer survivors with or without lymphedema. Finally, we analyzed tissue expression of IL-6 in matched biopsy samples obtained from lymphedematous and contralateral normal limbs of patients with lymphedema. Results: We found a significant elevation of IL-6 levels locally in regions of lymphatic fluid stasis in both the mouse tail model ($p<0.001$) as well as the mouse ALND model (p=0.009). Similarly, we found that serum levels of IL-6 were elevated in mice with tail lymphedema and after ALND as compared to sham surgical controls. These findings correlated with a statistically significant increase in local tissue expression of IL-6 expression ($p<0.001$) and activation of its downstream mediator STAT-3 in lymphedematous clinical samples as compared to matched contralateral normal biopsies. In addition, we noted significant increases in serum levels of IL-6 (p=0.004) in patients with lymphedema as compared with breast cancer survivors who did not have lymphedema. Conclusions: Lymphatic fluid stasis potently upregulates the expression of IL-6 both locally and systemically in mouse models of lymphedema as well as in patients with lymphedema. These findings suggest that serum levels of IL-6 may be a useful means of diagnosing lymphedema as well as assessing response to treatment.

P43

The Contralateral Unaffected Breast (CUB) as a Model for Studying Breast Cancer Risk D.A. Monahan,[1]* J. Wang,[2] N.M. Hansen,[1] K.P. Bethke,[1] S. Khan,[1] O. Lee,[2] E. Revesz,[1] N. Taft,[1] D. Ivancic,[2] C. Zalles.[3] *1. Division of Breast Surgery, Lynn Sage Comprehensive Breast Center at Northwestern Medical Center, Chicago, IL; 2. Northwestern University, Chicago, IL; 3. Kendall Medical Center, Miami, FL.*

The contralateral unaffected breast (CUB) as a model for studying breast cancer risk. Introduction: The CUB of breast cancer patients is at high risk for the development of second malignancies, which resemble the hormone receptor (HR) status of the index tumor. We have studied the feasibility of sampling the CUB for biomarker studies by performing random fine needle aspiration (rFNA) in the operating room during surgery for the index tumor. Methods: Women undergoing surgery for breast cancer between the years of 2006 and 2008 were enrolled in a prospective study in which rFNA of the CUB was performed. The rFNA specimens were submitted for cytologic analysis using the Masood score on 10% of the sample; histochemistry on 10% and RNA extraction (Trizol and RNeasy) on 80%. Expression of a panel of 28 selected genes was quantified using qRT-PCR (Ambion). Demographic and risk factors were recorded. Results: 83 women were enrolled (mean age 49 years, range 27-71); 40 (48%) were post-menopausal and 51 (61%) had HR positive breast cancer. The median epithelial cell yield was 280,000, median RNA yield was 283.2 ng and median RNA integrity was 7.6. Gene analysis was performed on 54 samples with sufficient RNA, 26 had ER negative index cancer and 28 had ER positive index cancer. The Masood score showed benign cytology in 4 women (score 6-10), proliferation without atypia (PWA) in 36 (score 11-14) and atypical cytology in 14 (score 15-18). We found 12 genes were differentially expressed in atypical samples compared to PWA samples. Among them, 8 estrogen-regulated genes were significantly increased in atypical samples ($p < 0.005$), including TFF1, AGT, PDZK1, PGR, GREB1, PRLR, CAMK2B, and CCND1. Conclusions: rFNA of the CUB is feasible, acceptable to women and produces high quality samples which can be used for gene expression analyses. The cytological changes between samples with atypia and without atypia are reflected in gene expression. The increase of estrogen-related genes may suggest estrogen plays a role on cytologic atypia.

Genes expressed at an increased rate in cytologic atypia.

Gene Symbol	Gene Name	Fold Change (atypia vs. w/o atypia)	P value
TFF1	trefoil factor 1	13.4	0.00083
AGT	angiotensinogen	10.9	0.0021
PDZK1	PDZ domain containing 1	10.2	0.00000053
PGR	progesterone receptor	9.4	0.000015
GREB1	gene regulated in breast cancer 1 protein	6.3	0.000024
GPR87	G protein-coupled receptor 87	4.6	0.0039
F3	coagulation factor III, thromboplastin	4.3	0.00019
PRLR	prolactin receptor	4.0	0.00015
CAMK2B	calcium/calmodulin-dependent protein kinase II beta	3.1	0.0025
CCND1	cyclin D1	2.6	0.00063
EEF1B2	eukaryotic translation elongation factor 1 beta 2	2.2	0.0000024
LCK	lymphocyte-specific protein tyrosine kinase	0.3	0.0015

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Sentinel Lymph Node Metastasis are More Likely to Develop in Triple Positive Breast Cancer Patients Without Compromising Disease Free Survival I. Rubio,* M. Espinosa-Bravo, J. Rabasa, A. Sao, I. Cebrecos, J. Xercavins. *Hospital Universitario Vall de Hebron, Barcelona, Spain.*

Background. Lymph node metastasis are the most significant prognostic factor for breast cancer (BC) patients and the use of sentinel lymph node biopsy (SLN) has generated an increased detection of positive nodes. Molecular subtypes have provided additional information on local recurrence and survival in BC patients. The objective of this study is to evaluate the correlation between axillary SLN metastasis and molecular subtypes in SLN in adjuvant and neoadjuvant BC patients and whether this may have prognostic implications. Methods. A total of 619 patients with clinically node negative T1-T3 breast cancer underwent SLN biopsy from 2005 to 2009. Patients were divided in two groups depending on the timing of SLN biopsy. Group 1 (493 patients) had surgery for first treament and group 2 (126 patients) had neoadjuvant treatment first. Patients

were classified according to ER/PR/Her2 status as (ER/PR/HER2 + (TP), ER/PR/HER2 – (TN), ER/PR/ + HER2 - and ER/PR - HER2 +). For SLN metastasis the following variables were tested in univariable and multivariate models: age, tumor grade, tumor type, and the combined hormone receptors and HER2. Results: The SLN was positive in group I in 150 of 493 patients (30.4 %) while in 50 of 126 patients (39.6%) in the neoadjuvant group (p <0.02). Altogether, 36 patients (7.9%) were classified as TP, 25 (5.5%) as ER/PR – HER2 +, 318 (69.9%) as ER/PR+ HER2 – and 76 (16.7%) as TN. Triple positive BC patients were more likely to have axillary SLN metastasis compared to other molecular subtypes (p = 0.02). Multivariate logistic regression revealed age (< 50 years) and TP tumors to be independent predictors of SLN metastasis. The 5-year disease-free survival rate for local regional and distant recurrences combined were 95% in group I vs. 85% in group II (p< 0.02). No statistically diferences were found in disease free survival by molecular subtypes. Median follow-up was 56 months. Conclusions. Her 2 overexpression favours SLN metastasis in ER/PR positive tumors over other ER/PR status. Differences in axillary involvement may not necessarily reflect differences in breast cancer outcomes.

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Post-operative Surveillance of Ductal Carcinoma *In Situ*

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Background: Although follow up imaging for invasive breast cancer is standardized, the appropriate post-operative screening for ductal carcinoma in situ (DCIS) has not been fully evaluated. Current practices include a 6 month interval mammogram for 2 years, which may be unnecessary. As such, it is critical to assess the utility of additional screening beyond a routine annual mammogram for patients with DCIS. Methods: Our pathology database was queried for the phrase 'ductal carcinoma in situ' from 2005 to 2010, and patients who underwent surgical excision were identified. Those without follow up imaging at our institution were excluded. Results: There were 87 patients who underwent excision for DCIS and proceeded with follow up. The median age was 57 years (range 36-87), and the median follow up was 2.7 years (range 0.02-7.5). Histologically, 10 lesions were ER-/PR-, while 66 were ER+/PR+. Re-excision was performed in 26 patients. On initial post-operative mammogram, 78 patients were assessed as BIRADS 1 or 2, which did not significantly correlate with a short interval of ≤ 200 days between surgery and imaging (p>0.05). Of the 70 short interval mammograms, 63 yielded benign findings, while 7 required additional imaging or intervention that ultimately resulted in benign findings, including 1 repeat excision for LCIS. To date, 82 patients have received at least one additional mammogram, and all subsequent findings have eventually been benign. There was no correlation between a short interval mammogram and DCIS grade, re-excision, or adjuvant radiation therapy (p>0.05). Patients with ER+/PR+ lesions or treated with endocrine therapy were less likely to undergo a short interval mammogram (p<0.05), despite the fact that all DCIS patients were recommended 6 month follow up. Conclusions: Although a clinical exam is still recommended at 6 months following surgical excision of DCIS, a short interval mammogram may be of questionable utility. In addition to psychological distress, this may lead to repeat imaging and procedures for ultimately benign lesions. Based on our findings, a 6 month follow up mammogram did not diagnose new or residual malignancy, and thus annual surveillance alone should be considered.

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Utility of Sentinel Lymph Node Dissection (SLND) in Ductal Carcinoma *In Situ* (DCIS)

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Introduction: The role of SLND in patients with DCIS remains a topic of debate. The incidence of positive sentinel lymph nodes (SLNs) in DCIS ranges from 2-13%, but the biological significance of such findings is unknown. This study sought to identify factors predictive of positive SLNs and evaluate the utility of SLND in patients with DCIS. **Methods:** Breast database query identified 1,321 patients with a final diagnosis of DCIS treated from 1993 to 2008 of whom 472 underwent SLND. We consider SLND in DCIS patients undergoing mastectomy or selectively in high-risk cases having an invasive component (size >2cm, high-grade, palpable). SLNs were categorized as isolated tumor cells (pN0[i+]: <0.2mm), micrometastasis (pN1mi: 0.2mm - <2mm) or macrometastasis (pN1: >2mm). Statistical analyses were performed to identify predictors of positive SLN findings. Changes in management such as axillary lymph node dissection (ALND), adjuvant chemotherapy (CTX) and radiotherapy (XRT) were examined. Mean follow-up time was 4.8 years for SLND and 6.0 years for the entire cohort. **Results:** Positive SLNs were present in 33 cases (7%): pN0(i+) = 25 (5.3%) and pN1mi = 8 (1.7%). No macrometastases were identified. Factors predictive of positive SLNs included DCIS size, biopsy method and total interventions defined as the sum of all biopsies and surgeries (Table 1). Overall, 7 (21.2%) patients with positive SLNs experienced a change in management: 2 pN0(i+) patients experienced ALND (n=1) or CTX (n=1) and 5 pN1mi patients experienced CTX (n=2) or ALND & CTX (n=3). No additional positive nodes were identified in the ALNDs. Patients treated with partial mastectomy received standard XRT. There were 2 local recurrences in the positive SLN group but no regional nodal recurrences. **Conclusions:** Positive SLNs were more likely in patients who underwent excisional biopsy and more than 3 total interventions. This may support the theory of benign mechanical transport of breast epithelial cells. The biological significance of these positive SLNs remains unknown; however these findings do not appear to impact prognosis. These data suggest that SLND is not warranted in all patients with DCIS.

Table 1. Clinicopathologic factors predictive of sentinel lymph node metastasis in DCIS patients

UNIVARIATE ANALYSIS

Characteristics	*Negative SLN (n=439)*	*Positive SLN (n=33)*	*P-value*
Biopsy method			0.04*
Percutaneous	332 (75.6)	19 (57.6)	
Excisional	107 (24.4)	14 (42.4)	
Surgery type			0.07*
Partial mastectomy	119 (27.1)	4 (12.1)	
Total mastectomy	320 (72.9)	29 (87.9)	
Size of DCIS			0.001
Mean	3.2	5.0	
Median (range)	2 (0.02-16.5)	4 (1-10)	
Grade			0.7*^
I	26 (6.0)	3 (9.1)	
II	174 (39.8)	13 (39.4)	
III	237 (54.2)	17 (51.5)	
Unknown	2	0	
Palpable tumor			0.4*
No	417 (95.0)	30 (91.0)	
Yes	22 (5.0)	3 (9.0)	
Total interventions			0.009#
Mean	2.6	3	
Median (range)	2 (1-8)	3 (1-5)	
5-year disease free survival	99.0%	100%	0.7

MULTIVARIATE ANALYSIS

Factor	*Odds Ratio*	*P-value*	*95% Confidence Interval*	
Biopsy method				
Percutaneous	Referent			
Excisional	3.7	0.002	1.6	8.7
Size of DCIS (cm)	1.2	0.004	1.1	1.3
Total interventions				
1-2	Referent			
3	2.4	0.07	0.9	6.1
>3	5.9	0.001	2.1	16.5

*Fisher's exact test; ^ Exclude unknown category, # Ranksum test

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Disparities in Access to Comprehensive Cancer Care: The Impact of Travel Distance on Utilization of Immediate Breast Reconstruction

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Background: There exist disparities in breast cancer care based on the distance traveled to treatment facilities. The relationship between utilization of immediate breast reconstruction (IBR) and travel distance (TD) has yet to be studied. Methods: Patients who underwent mastectomy for breast cancer were identified in the Pennsylvania Health Care Cost Containment Council database (2000-2004). A Student's t-test was performed to determine the relationship between TD and patient characteristics. Rates of IBR were examined by TD using a Chi Square test. A multivariable logistic regression model was developed to evaluate the association between TD and IBR with adjustment for age, estimated income, comorbid illnesses, and hospital teaching status. A subset analysis was performed on patients who underwent IBR to determine the relationship between

hospital teaching status and TD using a multivariable logistic regression model. Results: We identified 35,206 patients who underwent mastectomy during the study time period. Mean distance that patients traveled for care was 14.6 miles. Of patients who traveled <5 miles, mean age was 65.0 and mean estimated income was $51,307. Of patients who traveled >4 miles, mean age was 60.7 and mean estimated income was $57,0754 (p<0.01). The rate of IBR following mastectomy was 17.7% if TD<5 miles, 24.2% if TD=5-9 miles, 28.1% if TD=10-19 miles, and 28.7% if TD>19 miles (p<0.01). After adjustment for confounders, patients who traveled further were significantly more likely to undergo IBR when compared to patients who traveled <5 miles (5-9 miles: OR 1.16, 95% CI 1.07-1.26; 10-19 miles: OR 1.20, 95% CI 1.10-1.30; 20+ miles: OR 1.39, 95% CI 1.28-1.51). For patients who underwent IBR, the likelihood of being treated at a teaching hospital increased with greater distance traveled (10-19 miles: OR 1.28, 95% CI 1.12-1.46; 20+ miles: OR 1.60, 95% CI 1.40-1.82). Conclusions: Patients who traveled further were significantly more likely to undergo IBR. Efforts should be made to assist disadvantaged patients in accessing academic hospitals for comprehensive breast cancer care.

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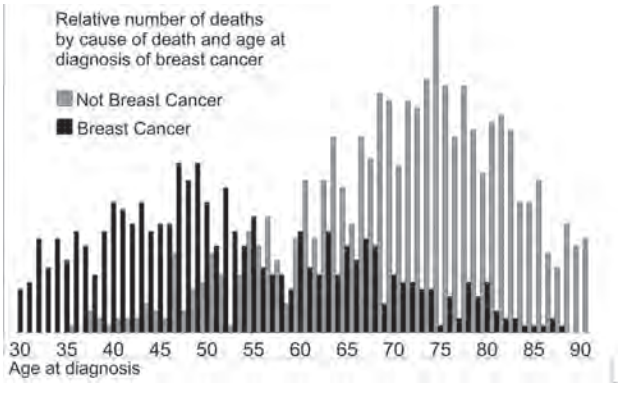
A Failure Analysis of Invasive Breast Cancer: Most Deaths from Disease Occur in Women Not Regularly Screened M.L. Webb,[1]* B. Cady,[1] J.S. Michaelson,[1] D.M. Bush,[1] K. Zabicki Calvillo,[2] D.B. Kopans,[3] B.L. Smith.[1] *1. Massachusetts General Hospital, Gillette Center for Women's Cancers, Breast Program, Boston, MA; 2. Brigham and Women's Hospital, Dana Farber Cancer Institute, Breast Oncology, Boston, MA; 3. Harvard Medical School, Boston, MA.*

Introduction: Mortality reduction from mammographic screening is controversial. Randomized population trials demonstrate mortality reduction of over 15% in women offered screening. In women actually screened, mortality reductions are greater. We hypothesized that breast cancer deaths predominately occurred in unscreened women. Methods: Invasive breast cancers diagnosed between 1990 and 1999 were followed through 2007. Data included demographics, mammography use, surgical and pathology reports, and dates of recurrence and death. Mammograms were screening or diagnostic based on absence or presence of breast signs or symptoms, and were substantiated by medical records. Deaths from breast cancer were defined only after documentation of prior recurrent disease. Death not from breast cancer was documented after absence of recurrent cancer and death from other causes. Results: Failure analysis of breast cancer defined 7301 patients diagnosed with breast cancer between 1990 and 1999, of which 2141 (29%) had died. The causes of death for 1705 (80%) of those cases were confirmed; 681 (40%) were caused by breast cancer while 1024 (60%) were due to other causes. Of those 681, the mammographic screening histories of 609 were determined by review of electronic medical records. Of women who died of breast cancer, 178 (29%) were regularly screened at intervals of two years of less; 118 (19%) of the cancers were screen-detected and 60 (10%) were interval cancers. The majority of women who died of breast cancer (431, 71%) were unscreened; 35 (8%) had a negative screening mammography more than two years before diagnosis and 395 (92%) had never had a mammogram. Women that died of breast cancer were diagnosed at a median age of 49 while those that did not die of breast cancer were diagnosed at a median age of 72 (Figure 1). Conclusion: Most deaths from breast cancer occur in women not mammographically screened. To maximize life years gained and reduction of mortality, screening before age 50 should be emphasized.



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Close and Positive Tumor Margins Management after Partial Mastectomy for Early Stage Breast Cancer Y.R. Alimi,[1] E. Bowman,[1] M. Mosunjac,[2] S.D. Perez,[1] W.C. Wood,[1] M. Rizzo.[1]* *1. Emory University, Department of Surgery, Atlanta, GA; 2. Emory University, Department of Pathology and Laboratory Medicine, Atlanta, GA.*

Introduction: Margin status is an important prognostic factor for local recurrence after breast conserving surgery (BCS) in patients with breast cancer. It is unclear and still controversial the definition of negative margins in breast oncology. Re-excision of tumor margins is necessary when the tumor is present at the inked margins. For patients with close margins, re-excision rates vary widely among surgeons and institutions. This study reviews the results of re-excision after BCS in cases of positive and close margins in a single Institution. Methods: We retrospectively analyzed patients who underwent BCS for ductal carcinoma in situ (DCIS) or infiltrating ductal carcinoma (IDC), Stage 0-II, from 2004 to 2007. Based upon the distance from the tumor to the margin of resection, we classified the margins as negative (≥1 mm), close (< 1 mm), or positive when tumor cells were at the inked margin. Results: Of 463 cases analyzed, mean age of 57.8 years (range 33- 89), 323 (69.7%) had negative margins after the first operation. 140 patients had either close (n=102, 22.0%) or positive margins (n=38, 8.2%) as shown in Table 1. The presence of DCIS, either alone or associated with IDC, increased the risk of close or positive margins (p=0.004). The majority of the patients with positive or close margins underwent additional surgery (n=98, 70%). The patients with tumor transected at the ink, chose mainly as a second operation a mastectomy (n=23, 60.5%). In patients with close margins, 39 (38.2%) refused an additional operation, 8(7.9%) opted for a mastectomy and 55 (53.9%) underwent margins re-excision. The majority of patients with close margins undergoing re-excision (n=43, 78.1%) had no residual tumor. Conclusion: This study suggests that in cases of close margins after BCS for early stage breast cancer, additional margin re-excision may not be necessary all the times. The advantages of this approach include improved patient satisfaction and decreased cost.

Table 1: Histological subtypes and Outcomes after Positive / Close Margins

Total (n=463)	Negative margins > 1mm (n=323, 69.8%)	Close margins < 1mm (n=102, 22.0%)	Positive margins at the ink (n=38, 8.2%)	p-value
IDC (n=184)	142	36	6	0.004*
DCIS (n=168)	107	47	14	
IDC+DCIS (n=85)	56	15	14	
ILC (n=20)	12	4	4	
No residual (n=6)	6	--	--	
No re-excision (n=44)	n/a	39	5	
Re-excision of margins (n=65)	n/a	Still positive 12** No residual 43	Still positive 6*** No residual 4	
Mastectomy (n=33)	n/a	8	23	

IDC= infiltrating ductal carcinoma
DCIS= ductal carcinoma in situ
IDC+DCIS= Patient with DCIS component >25% associated with IDC
* DCIS alone or associated with IDC increased the risk of close/positive margins using chi-squared test
** Three patients underwent mastectomy after first still positive re-excision
*** Patients refused additional surgery

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Risk Factors for Delayed Completion of Breast Conservation Therapy C.E. Loveland-Jones,* A.P. Close, V.W. Osborn, J.A. Montes, D.M. Nick, R.E. Taviera, B. Micaily, A. Davey, A. Willis. *Temple University, Philadelphia, PA.*

Introduction: There is evidence that delayed completion of breast conservation therapy (BCT), as defined by breast-conserving surgery followed by radiation therapy (XRT) for breast cancer, increases local recurrence and worsens survival. The purpose of this study was to determine risk factors for delayed completion of BCT. Methods: This was a retrospective cohort study conducted at a single institution. All female BCT patients from 2004-2010 were eligible, except those who received neoadjuvant/adjuvant chemotherapy. A time interval between surgery and the start of XRT >12 weeks and a duration of XRT >7 weeks were considered prolonged. An overall delay in BCT was defined

as a time interval >19 weeks. Age, ethnicity, insurance, body mass index (BMI), diabetes and tobacco were investigated as risk factors. Fisher's Exact and Chi-Square tests were used to compare groups, with $p<0.05$ considered significant. Results: A total of 148 women were included in the analysis. The majority had stage I ER/PR positive breast cancer. The only significant risk factor for a prolonged surgery-XRT interval was Medicaid (p=0.03). A total of 23.7% of Medicaid patients had a prolonged surgery-XRT interval, compared to 7.6% and 7.7% of Medicare and private insurance patients, respectively. Significant risk factors for prolonged XRT duration were age <65 years (p=0.01), Medicaid (p=0.004) and BMI>30 (p=0.02). A total of 38.0% of patients <65 years had a prolonged XRT duration, compared to 16.9% of patients ≥65 years. A total of 47.4% of Medicaid patients had a prolonged XRT duration, compared to 21.5% and 15.4% of Medicare and private insurance patients, respectively. A total of 34.1% of patients with a BMI>30 had a prolonged XRT duration, compared to 16.7% of patients with a BMI<30. Finally, the only significant risk factor for an overall BCT delay was Medicaid (p=0.02). A total of 23.7% of Medicaid patients had an overall delay, compared to 6.3% and 7.8% of Medicare and private insurance patients, respectively. Conclusion: Medicaid, age <65years and BMI>30 are risk factors for delays during BCT. These patients warrant close attention to ensure they do not have increased local recurrence and worsened survival.

Risk Factors for Delayed Completion of Breast Conservation Therapy

Risk Factor		Prolonged Surgery - XRT Interval (%)	p value	Prolonged XRT Duration (%)	p value	Overall Delay in Completion of BCT (%)	p value
Age	<65 yrs	16.9	0.1	38.0	**0.01**	15.4	0.2
	≥65 yrs	7.8		16.9		7.8	
Ethnicity	White	7.1	0.6	17.9	0.5	7.1	0.7
	Black	12.1		28.6		12.1	
	Latina	18.5		33.3		14.8	
	Arab	0.0		0.0		0.0	
Insurance	Medicaid	23.7	**0.03**	47.4	**0.004**	23.7	**0.02**
	Medicare	7.6		21.5		6.3	
	Private	7.7		15.4		7.8	
BMI	>30	13.6	0.6	34.1	**0.02**	14.8	0.2
	≤30	10.0		16.7		6.7	
Diabetes	Yes	9.0	1.0	36.4	0.3	9.0	1.0
	No	12.7		25.4		11.9	
Tobacco	Never	11.3	0.2	25.4	0.2	9.9	0.2
	Current	20.6		38.2		20.6	
	Past	8.8		20.9		7.0	

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Evaluating the Necessity of Preoperative Lymphoscintigraphy for Sentinel Lymph Node Biopsy in Breast Cancer M.G. Mount,* N.R. White, C.L. Nguyen, R.K. Orr, R.B. Hird. *Surgery, Spartanburg Regional Healthcare System, Spartanburg, SC.*

Introduction: The presence of axillary lymph node metastasis is the best predictor of survival in breast cancer patients. Sentinel Lymph Node Biopsy (SLNB) has been shown to accurately assess nodal disease. Preoperative lymphoscintigraphy (PL) is commonly performed for breast cancer patients undergoing SLNB. Recent articles have questioned the necessity of preoperative lymphatic mapping. Methods: 387 consecutive patients with clinically node negative breast cancer who underwent SLNB with PL at a single institution were included. Data were retrospectively collected regarding lymphoscinitgraphic findings and pathologic tumor characteristics. Tc-99m Sulfur colloid was injected in the nuclear medicine department either the day before or the day of surgery. Lymphoscintigraphy images were obtained within thirty minutes of radiocolloid injection. Sentinel Lymph Nodes (SLN) were defined as nodes that had gamma counts of at least 10% of the hottest SLN or evidence of blue dye staining. Axillary lymph node dissection (ALND) was performed if the SLN could not be identified. Students T-test and X2 test were used for statistical analysis. Results: PL revealed an axillary sentinel node in 270 of 387 patients (69.7%). In patients in whom PL was positive, SLN was identified in 270/270 patients (100%) compared to 113/117 (96.6%) in PL negative patients (p=0.002). Average 3.24 SLN were identified in PL positive patients versus 2.66 SLN in PL negative patients (p=0.004). SLN was positive in 63/270 (23.3%) of patients with positive PL. SLN was positive in 31/113 (27.4%) of patients with negative PL (p=0.51). Of the four patients in the negative PL group in whom the SLN was not identified, 2/4 (50%) had positive nodes at ALND. Conclusions: A high rate of sentinel lymph node identification can be obtained despite negative preoperative lymphoscintigraphy results. Although positive PL may predict a greater number of sentinel lymph nodes obtained, rates of SLN positivity do not differ from patients with negative PL. Preoperative lymphoscintigraphy may not be necessary for performance of successful sentinel lymph node biopsy.

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Cyclooxygenase-2 Signaling in Breast Cancer-initiating Cells C. Hall,* B. Laubacher, A. Walker, S. Massingill, A. Lucci. *Surgical Oncology, Unit 0107, UT MD Anderson Cancer Center, Houston, TX.*

Introduction: Only a small fraction of breast tumor cells, "breast cancer-initiating cells" (CSC), have the ability to initiate tumor growth and metastasis. Some characteristics of breast CSCs have been described in vitro by employing non-adherent CSC-enriching culture conditions. Little is known regarding prostanoid signaling or prostaglandin E2 (PgE2) production in CSCs. In this study we measured cyclooxygenase-2 (COX-2) and prostaglandin E2 receptor expression in CSCs and assessed the effects of COX-2 and Ep4 inhibition on in vitro CSC spheroid formation and PgE2 production. Methods: CSCs were cultured in serum-free medium using ultra-low attachment plates. Cells were treated with vehicle, a COX-2 inhibitor (Celecoxib), or an EP4 inhibitor (GW627368X) at concentrations of 0.1, 1, 10, or 100uM for 10 days. MCF-7 and SUM149 spheroids were quantified using a Gelcount machine; MDA-MB-231 cells were counted manually. Western blots were performed using anti-COX-2 and anti-EP1/2/3/4 antibodies. Prostaglandin E2 production was measured using an immunoassay kit (Cayman Chemical). Results: MDA-MB-231 and SUM149 CSCs exhibited COX-2 expression, EP2/EP4 protein was detected for MCF-7, MDA-MB-231, and SUM149 CSCs. Celecoxib IC50 values for MCF-7 and SUM149 CSC spheroid formation were 0.5 and 2.2uM, respectively; the IC50 value was 2.8uM for MDA-MB-231 cells. GW627386X IC50 values for MCF-7 and SUM149 CSC spheroid formation were 1.2 and 0.3uM, respectively, and 5.8uM for MDA-MB-231 cells. No significant differences in PGE2 production were observed for MCF-7 CSCs compared to adherent MCF-7 cells (11.5 ± 4.4 vs. 8.7 ± 2.1 pg/mL/106 cells; p=0.88). However, PgE2 production in MDA-MB-231 CSCs was significantly higher than adherent MDA-MB-231 cells (1507.0 ± 329.0 vs. 13.8 ± 5.7 pg/mL/106 cells; $p\leq0.001$) and SUM149 CSC PgE2 production was significantly higher than SUM149 adherent cells (4932.9 ± 501.7 vs. 194.5 ± 31.0 pg/mL/106 cells; $p\leq0.001$). 10uM Celecoxib treatment inhibited PGE2 production in MDA-MB-231 and SUM 149 CSCs. Conclusions: MDA-MB-231 and SUM149 CSCs express COX-2, EP2 and Ep4, and produce high levels of PGE2. CSC spheroid formation is significantly decreased with COX-2 and EP4 inhibition.

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Nipple Sparing Mastectomies, A Report of 200 Mastectomies in 111 Patients E. Busch-Devereaux,* A. Mishkit, R. Israeli, J.N. Romanelli, D. Yoon-Schwartz. *Surgery, North Shore-LIJ Huntington Hospital, Greenlawn, NY.*

Introduction: Nipple sparing mastectomies (NSM) are gaining in popularity as a more cosmetic option for both risk reduction and cancer treatment. We describe our experience. Methods: An Institutional Review Board approved retrospective/prospective database was formed for women having NSM. Data was collected on the procedure, indications, complications and follow-up. Results: One hundred eleven patients underwent 200 NSM between March 2007 and September 2012. Median follow-up is 19 months. Median age is 52 (range 24-74). Eighty-nine patients had bilateral NSM: 53 unilateral cancer with prophylactic contralateral mastectomy, 31 bilateral prophylactic, and 5 bilateral cancer. Twenty-two patients had a unilateral NSM: 15 cancer and 7 prophylactic. There are 24 BRCA carriers. Incision patterns used include circumareola-53.5%, circumareola with lateral extension-26%, variations of batwing-11.5%, and other-9%. Reconstructions were implant based in 88% and free flaps in 12%. Nipple areola complex (NAC) complications included: superficial epidermolysis-22.5%, 10-40% areola slough-2.5%, 50% nipple necrosis-1%, over 70% areola slough-0.5%, complete NAC necrosis-1%, and wound dehiscence-1%. One patient had ischemic NACs removed during NSM to allow re-creation of the areolae with flap skin. There were 6 infections, with implant loss in 3/176 (1.7%). One reoperation was needed for a hematoma. Superficial flap margins were positive in 4 NSM. Nipple cores had cancer in 4/80 (5%) NSM with cancer. Nipple sensation was documented in

114 NSM, the majority having little to none. Two incidental cases of DCIS were detected in the 122 prophylactic NSM. There have been 3 mastectomy flap recurrences near the original primary sites at 18,23 and 30 months (incidence of 3.8%). No recurrences have been seen in the NAC. One axillary soft tissue recurrence occurred at 20 months. Two patients have developed distant metastases. No cancers have developed in a prophylactic NSM site. Conclusions: NSM can be performed with a low incidence of significant areola or nipple loss through small cosmetic incisions. There have been no local recurrences in the NAC, however longer follow-up is needed to verify oncologic safety.

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A Comparison of Accelerated Partial Breast Irradiation with Whole Breast Irradiation in Patients with Pure Ductal Carcinoma *In Situ*
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Background: The efficacy of radiation in reducing in breast tumor recurrences (IBTR) in patients (pts) with ductal carcinoma in situ (DCIS) has been well established. Less is known about the clinical effectiveness of accelerated partial breast irradiation (APBI) in DCIS pts. We hypothesized that APBI would provide equivalent local control to whole breast irradiation (WBI) in pts with DCIS. Methods: Following IRB approval, a retrospective chart review from January 2004 to October 2011 identified 123 pts with DCIS treated with breast conserving surgery and radiotherapy. 83 patients received APBI via balloon brachytherapy(98%) or 3D-conformal(2%) and 40 pts with 41 cancers received WBI. Rates of recurrence were evaluated. Results: Median follow up was 38 months. The WBI cohort was younger and more likely to take hormonal therapy than the APBI cohort($p = 0.034$); otherwise the groups were similar with respect to tumor size, grade, estrogen receptor status, margin status and family history. There were 5(4%) IBTR at a median of 37 months. The 4-year actuarial IBTR rate was 3.8%. Of 83 APBI cancers, there were 3 IBTR (1 local, 2 elsewhere) compared to 2/41 (elsewhere) IBTR in the WBI cohort. There were no significant differences in the 4-year IBTR rates between pts treated with APBI versus WBI(3.4% vs. 4.2%, $p=0.66$). On univariate analysis, there was a trend towards a higher risk of IBTR with a positive family history(HR=6.1, $p=0.07$) and lack of hormonal therapy(HR=5.35, $p= 0.13$). Otherwise there was no association between age (<50 vs. ≥ 50), grade, margin status, or type of radiation and risk of IBTR. There were 2 regional(2.4%) recurrences in the APBI group at a median of 51 months compared to none in the WBI group. Conclusions: Pts with DCIS treated with APBI had low rates of IBTR that were comparable to WBI. Type of radiation was not associated with risk of IBTR. There was a slightly higher rate of regional recurrence in pts treated with APBI, although this may be related to tumor biology and not inferiority of APBI. Longer follow-up is needed to determine the safety of APBI in pts with pure DCIS.

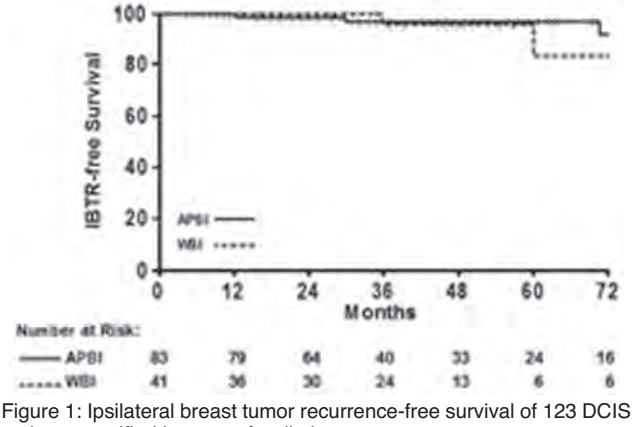

Figure 1: Ipsilateral breast tumor recurrence-free survival of 123 DCIS patients stratified by type of radiation

P55

The Prognostic Value of Additional Malignant Lesions Detected by Magnetic Resonance Imaging versus Mammography
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Background: Nodal positivity has been correlated with a poorer prognosis in breast cancer (BrCA). The addition of Magnetic Resonance Imaging (MRI) in BrCa evaluation has been shown to find additional lesions not seen on mammogram (MMG) in up to 15% of patients (pts). However, there is no clear data available comparing nodal positivity in pts with multiple lesions versus single lesions found on MRI and MMG. Hence, a study was composed to compare nodal positivity in pts with single versus multiple lesions found on MRI and MMG. Methods: A retroprospective study of BrCa pts undergoing MRI and MMG was performed. The main objective was to compare nodal positivity in pts with additional invasive lesions found on MRI versus single invasive lesions found on MRI or MMG. All pts underwent sentinel node mapping with 1% methylene blue. Results: A total of 425 pts were included in the study. The average number of sentinel lymph nodes in patients with single lesions was 2.46 versus 2.42 in patients with multiple lesions. The overall nodal positivity among invasive lesions was 23.8%. The pts with single malignant lesions had a nodal positivity rate of 21.2% versus 31.2% in pts with multiple lesions. Table I. MRI detected multiple lesions in 107 pts, 80 (18.8%) of which were not detected by MMG. Of these 80 pts, 36 (45%) were invasive, 36 (45%) were benign and 8 (10%) were in situ lesions. The nodal positivity in pts with additional malignant lesions detected by MRI was 47.2%. Contralateral malignant lesions were detected in 25 patients by MRI only with 20% nodal positivity. Comparing pts with single malignant lesions to pts with additional malignant lesions detected by MRI only, nodal positivity increased from 21.2% to 47.2% (p value < 0.006). Conclusion: Our study confirms that additional invasive lesions found on MRI had significantly higher nodal positivity compared with those with single invasive lesions. Hence, addition of MRI in early stage breast cancer may have prognostic value due to increased detection of nodal positivity.

	Single Lesions	Multiple Lesions		
	Single Breast Lesions detected by Both MRI and Mammogram	Detected by Both	Detected by MRI only	Total
Number of Patients	318	27	80	107
DCIS	49	6	8	14
Nodal Positivity	21.2%(57/269)	28.6%(6/21)	31.9%(23/72)	31.2%(29/93)
	Single Lesions	Ipsilateral Lesions	Contralateral Lesions	Total
Total Number of Patients	269	68	25	93
Nodal positive	57	24	5	29
Nodal positivity	21.2%	35.3%	20%	31.2%
	Additional lesions Detected by MRI only			
	DCIS	Benign	Malignant	Total
Number of patients	8	36	36	80
Nodal Positivity	0	20.7% (6/36)	47.2% (17/36)	31.9% (23/72)

P56

Risk of Lymphedema after Mastectomy – Potential Benefit of Applying Z11 Protocol to Mastectomy Patients
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BACKGROUND: Axillary lymph node dissection (ALND) and post mastectomy radiation (RT) is commonly recommended for mastectomy patients with positive sentinel lymph node biopsy (SLNB), but carries a high risk of lymphedema. Effective alternatives to ALND that reduce the risk of lymphedema are needed. We quantified rates of lymphedema in mastectomy patients who received SLNB with RT, compared to ALND with or without RT. METHODS: 526 patients who underwent 558 mastectomies as treatment for breast cancer from 2005-2012 were identified from patients prospectively screened for lymphedema at our institution. Arm measurements were performed via perometry pre-operatively and ≥3 months after surgery, median post-operative follow-up of 24 months (range 3-83). RT included chest wall +/- regional

nodal irradiation. Lymphedema was defined as ≥10% arm volume increase occurring ≥3 months from surgery, using relative volume change (RVC) for unilateral and weight-adjusted volume change (WAC) for bilateral mastectomy cases. Kaplan-Meier and Cox regression analyses were performed to determine rates of lymphedema and to identify risk factors. RESULTS: Mastectomies were categorized into four groups, 52% (288/558) SLNB-no RT, 5% (27/558) SLNB+RT, 11% (62/558) ALND-no RT, and 32% (181/558) ALND+RT. At 24 months median follow-up, rates of lymphedema were 11% (3/27) after SLNB+RT compared with 24% (44/181) after ALND+RT ($p < 0.0001$), and 15% after ALND without RT ($p = 0.03$) (Figure 1). SLNB-no RT had the lowest rate of lymphedema at <1% (1/288). By multivariate analysis, the risk of lymphedema varied significantly by RT (p=0.00012), type of axillary surgery (p=0.002), and BMI (p<0.0001). CONCLUSION: Patients who require post-mastectomy RT after ALND remain at highest risk for developing lymphedema. Avoiding completion ALND and instead receiving SLNB with RT would significantly reduce the risk of lymphedema. Future trials should investigate the safety of applying the Z-11 protocol to patients requiring mastectomy to reduce lymphedema risk.

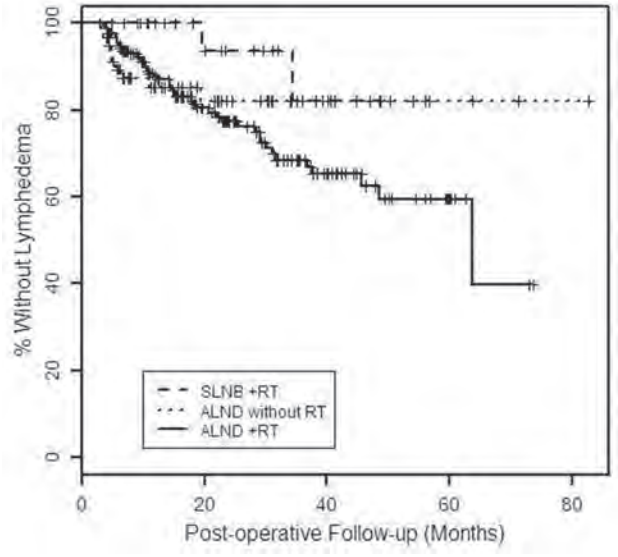

Figure 1. Risk of lymphedema after mastectomy

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WITHDRAWN

P58
One Day Core Needle Biopsy in a Breast Clinic: 4-Years Experience

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Introduction: Many attempts have been made to combine the high diagnostic accuracy and conclusive rate of core needle biopsy (CNB) with the speed of fine needle aspiration cytology (FNAC) in evaluation of solid breast lesions. Multiple hybrid techniques have been developed to achieve this, including Touch Imprint Cytology (TIC) and Core Wash Cytology (CWC). We describe a cohort of patients with suspicious breast lesions for whom we used a relatively new, accelerated method of CNB processing utilizing microwave technology, to make a definitive histologic diagnosis on the same day. Materials and methods: all patients visiting our breast clinic during a four year period were reviewed to identify all CNBs in this period performed in a same day diagnosis track. CNB result was compared to post-operative pathology reports, when available, and to follow-up when patients were not surgically treated. Results: 3543 patients visited our breast clinic, 1060 of these patients underwent CNB of 1383 lesions, 898 of which in a same day diagnosis track. In the same day diagnosis group we identified 351 malignant- and 547 benign lesions. Benign lesions had a mean follow up of 27.8 months (range 6-54 months), revealing four possible false-negative cases. Twenty five patients diagnosed with a malignancy were not treated surgically but received only palliative chemotherapy. Post-operative results are shown in table 1. The accelerated CNB processing technique has a sensitivity of 96.9% and a specificity of 99.4%. The inconclusive rate was 9.2%. Conclusion: For a same day diagnosis for solid breast lesions, a conclusive diagnosis was given with accelerated CNB processing in 65% of the patients requiring biopsy. This technique can be used reliably in a same day diagnosis breast clinic with a very high sensitivity, specificity and conclusive rate.

Lesions with a same day diagnosis (surgically treated cases only

		Post operative result			
		Benign	High risk	Ductal Carcinoma In Situ	Invasive cancer
Core Needle Biopsy result	Benign	62	2	1	2*
	High risk	1	2	0	0
	Ductal Carcinoma In Situ	0	1	13	3
	Invasive Cancer	2#	0	2	304

*both phyllodes tumors, one borderline malignant, one high grade malignant
#one case of complete response to neo-adjuvant therapy

P59
Breast Pathology Review: Does it Make a Difference?

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Introduction: Breast pathology is a challenging subspecialty and previous work has shown discrepancies in breast pathology diagnoses even among specialists. The accurate diagnosis of breast cancer and benign disease can strongly impact management and decision-making, both surgical and for adjuvant therapy. We assessed the role of breast pathology second opinions by breast cancer pathology specialists at our institution and the incidence of change in diagnosis and management. Methods: Cases referred after breast biopsy for surgical opinion to a single institution over the course of two years (Jan 2010- Jan 2012) were identified. Surgical pathologists with expertise in breast disease reviewed slides submitted from the primary institution and rendered a diagnosis (second opinion). Paired comparison of these reports was performed for evaluation of change in diagnosis and management. Results: A total of 306 cases were reviewed comprised of 268 core needle biopsy and 38 excisional biopsy specimens. Change in diagnosis was documented in 59/306 (19%) cases, and of these cases, 35/59 (59%) resulted in a change in definitive management. Changes in diagnosis were categorized into groups presented in the table below. The most common change in pathology opinion was from one benign condition to another 36/59 (61%),with 21/36 (58%) of these resulting in change in management regarding excision. The likelihood of change in diagnosis did not differ when comparing type of institution from which pathology originated: change was observed in 27/128 (21%) of consults originating from other University hospitals, 23/104 (22%) from Community hospitals, and 9/74 (12%) from Commercial laboratories (p=NS, 0.13). Change in management was indicated in 19/128 (15%), 11/104 (11%), and 5/74 (7%) of consults from the same groups respectively (p=NS 0.18). Conclusion: Further review of surgical pathology specimens by specialized breast pathologists alters diagnosis and management in a significant proportion of cases regard-

less of original institution type. Pathology consultation should remain an essential component of patient evaluation for second opinion regarding treatment of breast disease.

Changes in pathology diagnosis and management

	Change in Diagnosis (n=59)	Change in management (n=35)
Benign to benign*	36/59 (61%)	21/35 (60%)
Benign to DCIS	10/59 (17%)	10/35 (29%)
DCIS to invasive cancer	3/59 (5%)	3/35 (9%)
invasive ductal to invasive lobular cancer	9/59 (15%)	0/35 (0%)
Axillary node status	1/59 (2%)	1/35 (3%)

* This category includes changes from benign lesions recommended for excision (LCIS, atypia, radial scar, papillary lesion) and benign lesions not requiring excision (fibroadenoma, fibrocystic changes, and ductal hyperplasia)

P60

Trends in Neoadjuvant Chemotherapy for Surgical Breast Cancer Patients in the United States H.F. Schoellhammer,* L. Streja, L. Kruper, C. Vito, J. Yim, S.L. Chen. *Surgery, City of Hope National Medical Center, Duarte, CA.*

Background: Reports on the potential value of neoadjuvant chemotherapy (NAC) for breast cancer have increased over the past decade; however, details regarding the adoption of NAC over time in the general breast cancer population is unknown. Our study aims to examine national and regional trends in the use of NAC for breast cancer, and to identify predictors for the use of NAC. Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for invasive breast cancer patients diagnosed from 2004-2009 treated surgically in the United States. Since direct NAC data is not provided in SEER, we used the tumor and node evaluation fields identifying when pathologic assessment was performed relative to systemic treatment as a proxy for NAC. Patient characteristics evaluated include age, sex, race, ethnicity, tumor size, nodal status, and estrogen (ER) and progesterone receptor (PR) status. Trends in NAC were assessed overall, by region, and by patient characteristics using Jonckheere-Terpstra two-sided test for trend. Multivariate logistic regression models were analyzed to identify predictors of NAC use. Results: We identified 264,699 patients from SEER that fit the inclusion criteria. Overall, rates of neoadjuvant therapy increased from 4.7% in 2004 to 5.9% in 2009 ($p<0.0001$) and 8.6% to 11.5% for patients with traditional NAC indications ($p<0.0001$). Regions show significant increasing trend of varying degrees from 2004 to 2009 (all p-values <0.0001): Southwest (4.5% to 8.1%), Pacific Coast (4.3% to 5.6%), and East (4.7% to 5.8%). Changes in the Northern Plains were not significant (8.0% to 7.1%, $p=0.41$). Predictors of NAC in the multivariate logistic model include younger age, non-white race, year of diagnosis, larger tumor size, ER-, PR-, positive nodal status, region and the following interactions: tumor size and nodal status, year and region, year and ER-, year and nodal status, tumor size and region (all p-values <0.001). Conclusion: Despite increased interest in NAC for surgical breast cancer patients, rates of use have only modestly increased, and rates of change vary by region. Further study to elucidate reasons for trends in NAC use is warranted.

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Treatment of the Metachronous Contralateral Breast Cancer: SEER Study of Factors Affecting Surgical Choice J. Young,* N. Watroba, A. Groman, S. Kumar, S.B. Edge. *Rowell Park Cancer Institute, Buffalo, NY.*

Introduction: About 10% of women with breast cancer (BC) develop a contralateral BC in their lifetime. Data on patterns and factors that affect surgical therapy of the second cancer are limited. This study used the Surveillance Epidemiology and End Results (SEER) registry to identify women with metachronous bilateral breast cancer, define patterns of surgical care, and identify the factors that may affect type of treatment. Methods: The SEER registry was searched for women with BC diagnosed between January 1992 and December 2008 who had a metachronous contralateral BC defined as >6 months between diagnoses. Those with stage IV BC at the first cancer, or who had unknown surgery type for the first BC were excluded. Clinicopathologic and demographic factors were examined by backward selected multivariate logistic regression for association with type of surgical therapy of the second BC, defined as breast-conserving (BCT) or mastectomy. Results: Among 15,013 women with metachronous bilateral BC, the median time between BC diagnoses was 58.3 months. Type of surgery for the 1st BC was the most significant factor associated with surgery type for the 2nd BC. 66.7% of patients treated with BCT for the 1st BC were treated with BCT for the 2nd BC; and 74.7% of patients who were treated with mastectomy for the 1st BC were treated with mastectomy for the 2nd BC ($p=<0.001$). Factors associated on multivariate analysis with use of mastectomy for the 2nd BC are shown in the Table, including mastectomy at 1st BC (OR 6.42), T3 cancer 2nd BC (OR 10.92), Tis cancer at 2nd BC (OR 1.34), no nodes examined at 2nd BC (OR 0.17). Patients were slightly less likely to have a mastectomy as the year of the first diagnosis increased (OR 0.99, $p=0.047$), as the year of second diagnosis increased (OR 0.98, $p<0.001$) and age at diagnosis increased (OR 0.99, $p<0.001$). Conclusion: The choice of surgery for the second contralateral metachronous breast cancer was largely dependent on the type of surgery for the first cancer. Factors increasing likelihood of mastectomy for the 2nd BC were the size of tumor, stage, younger age and race.

Factors Associated with Mastectomy for the 2nd Breast Cancer

	Odds Ratio (95% CI)	
	Univariate	Multivariate
Mastectomy for 1st BC	7.82 (7.25, 8.44)	6.42 (5.73, 7.19)
Tis cancer 1st BC	0.95 (0.87,1.03)	1.22 (1.08, 1.37)**
Tis cancer 2nd BC	0.00 (0.83, 0.97)	1.34 (0.97, 1.85)
T3 cancer at 2nd BC	6.67 (5.10, 8.73)	10.92 (7.88, 15.13)
No nodes examined 2nd BC	0.32 (0.29, 0.34)	0.17 (0.15, 0.19)
African American race	1.02 (0.91, 1.14)*	0.73 (0.62, 0.86)

All $p<0.001$ except as note *p=0.022 **p=0.034

P62

What Percent of DCIS of the Breast is Calcified? B.K. Killelea,* A. Chagpar, M. Dixon, T. Tsangaris, N.R. Horowitz, J.D. Bishop, D.R. Lannin. *Surgery, Yale University School of Medicine, New Haven, CT.*

Objectives: Pure DCIS is now almost always diagnosed following identification of suspicious mammographic calcifications, whereas DCIS associated with invasive cancers is frequently not calcified. The purpose of this study was to determine what proportion of DCIS is calcified and how the characteristics of calcified and non-calcified DCIS differ. Methods: A retrospective review of the prospectively maintained breast database at our institution was performed to identify all patients diagnosed with DCIS from 2003-2011 with or without an invasive tumor. Mammogram reports were reviewed to determine whether calcifications were present. Results: There were 1184 cases of DCIS (70% associated with an invasive component), of which 601 (51%) were associated with calcifications seen on mammogram, and 583 (49%) had no associated calcifications. The presence of calcifications was strongly associated with the extent of the DCIS component, comedo and micropapillary histology, the presence of necrosis, and the grade of the DCIS ($p<0.001$ for each). (Table 1) High grade DCIS was almost twice as likely to be calcified compared with low grade DCIS. All of these variables remained independently associated with the presence of calcifications in multivariable models. Neither race, age, nor hormone receptor status was associated with the presence of calcifications. Conclusions: Approximately half of the DCIS in this study was not associated with mammographic calcifications, but this varied markedly by grade. The incidence of low grade invasive tumors in the SEER database has increased dramatically over the past 4 decades, whereas the incidence of high grade invasive cancers has

slowly decreased. Because high grade DCIS is often calcified, a significant percentage is detected by screening mammography and surgically excised, and this may account for the decrease in high grade invasive tumors. In contrast, there may be a large reservoir of low grade, non-calcified DCIS that is not being detected by current breast imaging. Future study is needed to determine the clinical relevance and optimal management of this low grade, non-calcified DCIS.

Calcifications by characteristics of the DCIS

	Percent calcified (no.)	P value
Overall	51% (601/1184)	---
Extent of DCIS vs. invasive		<0.001
DCIS only	82% (276/337)	
Extensive	55% (102/186)	
Average	35% (174/493)	
Minimal	17% (23/138)	
Grade		<0.001
1	35% (51/147)	
2	46% (256/555)	
3	61% (272/447)	
Necrosis		<0.001
No	32% (128/400)	
Yes	61% (417/683)	
Histology*		
Comedo	78% (114/147)	<0.001
Micropapillary	63% (91/144)	<0.001
Solid	52% (348/663)	ns
Cribiform	52% (346/662)	ns
Flat	60% (35/58)	ns
Papillary	47% (51/109)	ns

* many cases had more than one histology

P63

Why Women are Now Choosing Mastectomy: The Surgeon's Perspective A.M. Covelli,[1]* N. Baxter,[2] M. Fitch,[3] F. Wright.[3] *1. Institute of Health Policy, Management and Evaluation at the University of Toronto, Toronto, ON, Canada; 2. Li Ka Shing Knowledge Institute at St. Michael's Hospital, Toronto, ON, Canada; 3. Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Mastectomy (ipsilateral and contralateral), as treatment for early-stage breast cancer (ESBC) has been increasing since 2003. Studies suggest this is due to women playing an active role in their decision-making, as well as the perception that mastectomy is the preferred treatment by their surgeon. No study has qualitatively explored the surgeon's role in the increasing rates. To understand the surgeon's current practice and perception of the increasing mastectomy rate we conducted an exploratory qualitative study. Semi-structured interviews were completed with general surgeons across Ontario, Canada. Our sample varied in length/location of practice, extent of training, and gender. Interviews continued until data saturation was reached. Key ideas and themes were identified by two independent coders. A total of 23 general surgeons participated in one-on-one telephone interviews. Seven key themes emerged: 1. Discussing the diagnosis: surgeons discussed mastectomy and lumpectomy with patients, including evidence based recommendations. 2. Discussion of recurrence and survival: difficult to convey and poorly understood by patients 3. Health care delivery: varied use of MRI, variable access to reconstruction across the province 4. Perceptions why women choose unilateral mastectomy: concerns around mortality, recurrence, and effects of radiation 5. Perceptions why women choose contralateral mastectomy: misinformation regarding incidence of contralateral cancer and desire for cosmetic balance 6. Perception of increasing mastectomy rates varies with location of practice: no change noted within the community, increasing within academic centres. 7. Information seeking and influences other than the surgeon: patients are not sharing their influential outside sources of information; including previous cancer experience. Despite discussing both treatment options, surgeons working in high volume centres observed an increasing rate in mastectomy. Choice for mastectomy is often due to fear and misinformation, with recurrence and survival rates being poorly understood. Better understanding patient sources of information and fears around survival would benefit surgical discussions with breast cancer patients.

Increasing Mastectomy Rates: A Thematic network of illustrative quotes from the surgeon interviews describing their current practice and perception of the increasing mastectomy rates. Numbers in parenthesis indicate surgeon interview I.D.

P64

Preoperative Axillary Ultrasound (AUS) for Identification of Sentinel Lymph Nodes in Breast Cancer P.B. Wehner,* K. Kopkash, A. Woodworth, V. Kent, J. Lang, H. Silberman, H. Macdonald, P. Sheth, S.S. Sener. *University of Southern California, Pasadena, CA.*

Background. Published reports have confirmed the ability of AUS to identify axillary lymph node metastases, but the question of whether AUS can locate the sentinel lymph node, regardless of whether it contains cancer, remains unanswered. The purpose of this study was to determine the frequency with which suspicious lymph nodes identified by preoperative AUS were sentinel versus non-sentinel nodes. Methods. Patients with invasive breast cancer who were clinically node-negative had breast and axillary ultrasound as part of surgical planning. The exams were done by dedicated breast radiologists,using a 12 MHz linear array transducer (HDI 5000: Philips Ultrasound). Ultrasound-guided core biopsies were done using a 16 g spring-loaded core biopsy device (16g MD TECH SuperCore). A retrospective analysis of records from September 2009 through August 2012 was performed for invasive breast cancer patients who had sentinel lymph node biopsy (SLNB) accompanied by wire-localization of suspicious nodes (BIRADS 4 or 5), which had been identified by preoperative AUS and for which there were discordant (i.e., benign) core biopsy results. Until recently, patients with malignant core biopsy results had level I/II axillary lymph node dissection without SLNB. Results. The wire-localized lymph node was the sentinel node in 25 (83%) of 30 patients. Cancer was identified in sentinel lymph nodes of 3 patients, 2 of whom had the sentinel node accurately identified by AUS. For all 4 patients who had neoadjuvant chemotherapy, the node identified by AUS was a benign sentinel node. Conclusions. In this preliminary study, AUS identified the sentinel node in the majority of patients. These results, if confirmed in a larger patient sample size, would suggest that preoperative core biopsy guided by the combination of AUS and lymphatic mapping using technetium 99m sulphur colloid could potentially eliminate the need for axillary surgery in patients with benign core biopsies.

P65

Circulating Tumor Cells Predict Survival after Neoadjuvant Chemotherapy in Non-Metastatic Breast Cancer A. Lucci,* C. Hall, M. Karhade, P. Mishra, A. Anderson, I. Bedrosian, H.M. Kuerer. *Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX.*

Introduction: Circulating tumor cells (CTCs) predict outcome in metastatic breast cancer, but less is known regarding their significance in non-metastatic patients. Furthermore, it is unclear if the presence of CTCs after completion of neoadjuvant chemotherapy (NACT) predicts worse outcome. The purpose of this study was to determine if CTCs identified after NACT predict worse outcome. Methods: Clinical stage I-III breast cancer patients seen at a

single tertiary cancer center provided informed consent to participate in an IRB-approved study involving collection of blood (7.5 ml) at the time of surgery for their primary breast cancer. CTCs were detected using the CellSearchTM system. A positive result was defined as the presence of one or more cells per 7.5 ml blood. Statistical analyses used chi-square and Fischer's exact test. Results: One hundred and thirty seven patients were prospectively enrolled. Median age was 52 years and median follow-up was 34 months. Nine percent of patients had T1 disease, 36% T2, 20% T3, and 35% T4. Fifty-four percent of patients (73/137) had ER positive and 38% (52/137) had PR positive disease. Thirty percent of patients (41/137) were HER-2 positive. Twenty eight percent (38/137) had triple-negative tumors. Sixty-eight percent (93/137) had lymph node positive disease. One CTC was found in 27% (37/137) of patients post-NACT, but its presence did not predict worse outcome (p=NS). Two or more CTCs were present in 9% (12/137) of patients. Of the 20 patients who relapsed, 6 had 2 or more CTCs (P=0.002), while of the 14 patients who died, 4 had 2 or more CTCs (P=0.001). Conclusions: The presence of two or more CTCs after NACT predicted worse relapse-free and overall survival in patients with stage I-III breast cancer.

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Factors Associated with Recurrence in Breast Cancer Patients Vaccinated with the HER2-Derived GP2 Vaccine A.F. Trappey,[1]* J. Berry,[1] T. Vreeland,[1] D. Hale,[1] A. Sears,[1] R.S. Dabney,[1] S. Ponniah,[2] S.A. Perez,[3] G.T. Clifton,[1] C. Hintz,[2] J.D. Covelli,[2] M. Papamichail,[3] G.E. Peoples,[1] E.A. Mittendorf.[4] *1. Brooke Army Medical Center, San Antonio, TX; 2. Uniformed Services University of the Health Sciences, Bethesda, MD; 3. Saint Savas Cancer Hospital, Cancer Immunology and Immunotherapy Center, Athens, Greece; 4. University of Texas MD Anderson Cancer Center, Houston, TX.*

A phase I trial demonstrated GP2, an HLA-A2-restricted HER2 (654-662) peptide, to be safe and capable of stimulating CD8+cytotoxic T-lymphocytes (CTL) able to recognize and lyse HER2-expressing tumor-cells. We are conducting a phase II prospective, randomized, single-blinded, phase II trial of GP2+GM-CSF v GM-CSF for prevention of breast cancer (BC) recurrence. Here we present an analysis of immune and clinicopathologic factors that may impact recurrence. After completion of standard therapy; disease-free, node-positive or high-risk node-negative BC patients (pts) with any level of HER2 expression (IHC1-3+) were randomized to GP2+GM-CSF or GM-CSF in 6-monthly intradermal inoculations. Immunologic responses were measured pre-vaccination (R0) and post-vaccination (R6) using an in-vitro HLA-A2:Ig dimer assay to enumerate circulating GP2-specific CTL and in-vivo by delayed-type-hypersensitivity (DTH) reactions. Vaccinated patients that recurred (VR) were compared to non-recurred (VNR). To date, 49 patients have been vaccinated with 5 (10.2%) recurrences at a 2-year median follow-up. Comparing VR v. VNR, there were no significant differences noted with respect to age, percent of tumors ≥2cm, ER/PR-positivity, or high-grade tumors. VR pts had more positive-nodes (mean 6, VR v. 3, VNR; p=0.05) and fewer HER2-IHC3+ tumors (20% VR v. 50% VNR, p=0.20). VR pts had a less robust immunologic response to vaccination: mean R6 DTH 60% less than VNR (8.6 v. 22.5cm, p=0.20); no clonal expansion in VR by R0 v. R6 dimer (R0=0.72 v. R6=0.31, p=0.41) versus significant clonal expansion seen in VNR (R0=0.58 v. R6=1.1, p=0.001). Not surprisingly, demographic analysis of VR pts reveals they had larger tumors, more node positive disease and more ER/PR- tumors. They were, however, less likely to have HER2 3+ expression. VR pts also had less robust immunologic response to vaccination, suggesting immune response is a useful surrogate for cancer vaccine trials.

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Use of an Attenuated Version of a Strongly Immunogenic, Peptide-based Vaccine to Enhance an Anti-cancer Immune Response against Folate Receptor-α (FRα) T.J. Vreeland,[1] J.S. Berry,[1]* A.F. Trappey,[1] D. Hale,[1] G.T. Clifton,[1] A. Sears,[1] N.M. Shumway,[1] J.P. Holmes,[4] S. Ponniah,[3] E.A. Mittendorf,[2] C.G. Ioannides,[3] G.E. Peoples.[1] *1. Brooke Army Medical Center, San Antonio, TX; 2. University of Texas MD Anderson Cancer Center, Houston, TX; 3. Uniformed Services University of the Health Sciences, Bethesda, MD; 4. Department of Hematology and Medical Oncology, Naval Medical Center San Diego, San Diego, CA.*

BACKGROUND:FRα is over-expressed in ovarian and breast cancers. E39 (FBP 191-199) is an immunogenic, cytotoxic T lymphocyte (CTL) eliciting peptide derived from FRα used in a cancer vaccine strategy. Due to the in vitro observation of antigen-induced cell death with repeated T cell stimulation by E39, we developed an attenuated form of the E39, J65. We report the use of J65 alone or in combination with E39 to better induce E39-specific CTL and anti- FRα immunity. METHODS:T2 stabilization assays were performed using flow cytometry to determine peptide HLA-A2 binding affinity. Interferon-γ (IFNγ) release was measured from peripheral blood mononuclear cell (PMBC) cultures after weekly stimulation with J65x3 followed by re-stimulation with either J65 or E39. Naïve PBMCs from healthy donors (HD) were primed with weekly J65x3 or E39x3, re-stimulated with E39 at concentrations of 5 and 25μg/m, and then tested for the ability to lyse FRα-expressing cancer cells. PBMCs from responding donors (RD) were stimulated with E39 or J65, then proliferation was measured by cell counts after 14d. IL-2 secretion was also measured. RESULTS:The affinity of J65 for HLA-A2 was half that of the native E39 (65v130 MCF). After priming with J65x3, IFNγ levels were lower in the re-stimulated J65 culture compared to E39 re-stimulation (43v181 pg/ml). HD cultures demonstrated a higher tumor cell lysis (24.5 & 17.4% v 14.6 & 11.1%) after priming with J65x3 compared to E39x3. In RD cultures, PMBC cell counts were higher in the J65 culture compared with the same donor PMBCs stimulated with E39 (8.2x106v2.4x106 cells) and IL-2 concentrations were lower in the J65 cultures (820v580 pg/ml). CONCLUSIONS:In vitro analysis reveals the potential of J65 to induce CTL with the ability to proliferate while avoiding overstimulation. Importantly, these CTL demonstrate enhanced recognition and lysis of FRα-expressing cancer cells. The potential of this weaker, "survival inducing" version of E39 to induce a more robust anti-FRα immune response is currently being assessed in a first in human, phase 1b clinical trial in ovarian and breast cancer patients.

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Imaging Characteristics of Pleomorphic Lobular Carcinoma A. Sharma,* P. Ananthakrishnan, S.M. Feldman, B. Taback, A. Vaz. *Breast Surgery, Columbia University, New York, NY.*

INTRODUCTION: The pleomorphic subtype of invasive and in situ lobular lesions is a recently characterized variant of classical lobular carcinoma and confers a more aggressive pattern of behavior. Early identification of these lesions may aid in initiating prompt and appropriate treatment modalities. We reviewed our series of pleomorphic lobular lesions to evaluate the efficacy of mammography and ultrasonography in the assessment of patients with pleomorphic lobular carcinomas. METHODS: We retrospectively reviewed 95 cases of pleomorphic lobular invasive and in situ carcinomas of the breast from January 2008 to August 2012. Four patients were eliminated from our original cohort and of the 91 patients reviewed, 88 had mammographic imaging and 84 had ultrasonography. Images were reviewed by experienced breast mammographers. Tissue diagnosis was either determined by core biopsy and or surgical excision. Pathologic assessments were made by experienced breast pathologists. RESULTS: Retrospective analysis of imaging data determined that the most common mammographic and ultrasonographic finding was the presence of a mass. A suspicious mass was detected on mammography in 46.6% of cases and in 73.8% by ultrasonography. With respect to mammography, 26% of cases demonstrated pleomorphic or heterogeneous calcifications that were compatible with Breast Imaging Reporting and Data System (BI-RADS) 4 or 5 and 29.5% had architectural distortion or focal asymmetry. 9 out of 88 cases were mammographically negative and 17.8% were sonographically invisible. The overall sensitivity for mammography was 89.8% and 82% for ultrasonography. The overall number of pleomorphic lobular lesions detected by either of these two modalities was 74, and the overall sensitivity was 86%. CONCLUSION: Mammography and ultrasonography are useful imaging modalities in the evaluation of pleomorphic lobular carcinomas, both in situ and invasive. With the combined use of sonography and mammography, pleomorphic lobular carcinomas can be detected with an overall sensitivity of 86%.

Characteristics on Mammography and Ultrasound

Mammogram Finding	Total	Ultrasound Finding	Total
Spiculated Mass	16	Mass	62
Architectural Distortion or Focal Asymmetry	26	Negative US	15
Calcifications	23	Other US findings	7
Non-Spiculated Mass	25		
Negative Mammogram	9		

Table I is a tabulation of the imaging characteristics identified on mammography and ultrasound

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The Impact of High Expression of an ATP-binding Casette Transporter, ABCC11, in Breast Cancer Subtypes and Survival

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Purpose: The ATP-binding cassette transporters are known to play a role in multi-drug resistance. However, there have been conflicting reports regarding its clinical relevance with breast cancer, including recently identified ABCC11. We hypothesized that both the frequency and the levels of expression of ABCC11 in breast tumors differ with subtypes and are associated with prognosis. Methods: We constructed a tissue microarray (TMA) utilizing 281 breast cancer patient tumors and analyzed the expression of ABCB1, C1, C11 and G2 in the tumor by immunohistochemistry . Breast cancer subtype are also determined IHC of estrogen receptor, progesterone receptor and human epidermal growth factor receptor2 (HER2). For triple negative subtype, cytokeratin 5/6 and epidermal growth factor receptor were also used for further subdivision to core-basal or non-basal subtypes. Results were analyzed in clinicopathological characteristics, clinical follow-up and pathological complete response to neoadjuvant chemotherapy. Results: TMA contained breast cancer with 191 luminal A (68.0%), 17 luminal B (6.0%), 27 HER2 (9.0%) and 46 triple negative (16.4%) subtypes. ABCC1 and C11 has significantly worse disease free survival (p=0.027, p=0.003, respectively). The tumor with high expression of ABCC1, ABCC11, and ABCG2, but not ABCB1, were statistically more frequently and highly expressed in aggressive subtypes (p=0.011, p=0.004, p=0.010, respectively). High expression of ABCC11 in the cancer demonstrated trends toward decreased pathologic complete response rates to neoadjuvant chemotherapy. We have found that the aggressive subtypes, such as HER2 and triple negative tumors, had significantly frequent high expression of ABCC11 (p=0.027, p=0.003, respectively). Moreover, even among those patients with aggressive subtypes, ones with high expression ABCC11 demonstrated further significantly worse disease free survival (p=0.017, p<0.001, respectively). Conclusion: This is the first demonstration that ABCC1, C11 and G2 are highly expressed in aggressive breast cancer subtype and ABCC11 expression in breast cancer is associated with worse prognosis.

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Defining the Polo-Like Kinase 4 (Plk4) Interactome in Cancer

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High expression of Plk4, a serine/threonine kinase active from S through M phases of the cell cycle, indicates poor prognosis in breast, pancreas and colorectal cancer patients. Recent findings in our laboratory have shown a novel function for Plk4 in promoting cell migration; Therefore, our HYPOTHESIS is that Plk4 functions as an oncogene, enhancing cancer cell invasion by interacting with a defined group of proteins, an "interactome". Our present objective is to identify the proteins that mediate this Plk4 activity, in order to better understand the pathways and networks that facilitate metastatic capacity. METHODS: HeLa (human cervical cancer) cells were used as a model system to study the effect of Plk4 up- and down- regulation on motility-related phenotypes through transient transfection with Flag-Plk4 and Plk4 RNAi. Invasion through Matrigel was assessed using a Real Time Cell Analyzer (RTCA) system. HEK293 (human embryonic kidney) and HeLa cell lines stably expressing Plk4 upon tetracycline induction were generated and affinity purification mass spectrometry (AP-Mass Spec) was performed to identify the Plk4 interactome. RESULTS: A distinctive arborized spreading phenotype with increased number and length of filopodia was observed in Flag-Plk4 transfected HeLa cells compared to adjacent untransfected cells and to Flag-alone control, while Plk4 RNAi caused impaired spreading and a rounded cell morphology compared to Luciferase RNAi control. Decreased invasion was noted in Plk4-depleted HeLa cells compared to Luciferase control, while Plk4 overexpression increased invasion. Interaction proteomics identified several known and unknown Plk4 interacting proteins in Plk4-transfected cells, including centrosomal (Cep-152, Cep-192), microtubule-related (TUBB6) and actin-related (ARHGEF10, SRGAP1) proteins, in keeping with regulation of cytoskeletal dynamics. CONCLUSIONS: Plk4 enhances cancer cell spreading and invasion. AP-mass spec can be used to define the Plk4 interactome. Our results will inform the development of specific Plk4 inhibitors, which are currently being developed for clinical use in breast cancer patients, allowing selective targeting of cancers with Plk4-driven metastatic capacity.

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Increasing Yield of MRI Guided Breast Biopsy for Breast Cancer Determination

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Introduction: The inverse relationship between the sensitivity and specificity of MRI (MR) to detect breast cancer (BC) has made the modality controversial. Concerns over high rates of negative biopsies have dampened enthusiasm for the technique. Since 2006, the technical equipment and personnel involved in breast MR at our institution have not changed. We hypothesize that increasing experience with breast MR is associated with an increasing rate of cancer diagnosis following MR guided breast biopsy. Methods: The results of breast 211 consecutive MR guided biopsies in 194 patients at our institution (2006-2012) were reviewed retrospectively. The indications for breast MR were developed in 2006 prospectively by our breast cancer treatment team. In each instance described below, conventional breast imaging with digital mammogram, ultrasound and focused ultrasound based on the MR had failed to reveal a lesion that could be evaluated stereotactically or with ultrasound guided biopsy. Results: The initial indications for breast MR among 194 patients in this series were: axillary metastases with unknown primary, n=6; cancer staging evaluation, n=74; indeterminate mammogram/ultrasound, n=38; high risk screening, n=59; breast symptoms, n= 17. The overall results of the 211 MR breast biopsies were: benign (n=114, 54%); indeterminate (eg. papilloma, atypia, radial scar) (n=38, 18%); BC (n=59, 28%). The rate of MR biopsy showing BC varied by respect to the initial indication for the breast MR: axillary metastases from an unknown primary, 83%; cancer staging evaluation, 36%; indeterminate mammogram/ultrasound, 27%; high risk screening, 17%; breast symptoms, 5%. During the period of study, the rate of BC diagnosis resulting from MR biopsy increased significantly (2006-2007, n=62) 19%, (2008-2009, n=81) 28%, (2010-2012, n=68) 35%. Conclusions: The rate of detecting breast cancer on MR biopsy is related to the indication for breast MR. Importantly, increasing experience with breast MR is resulting in better patient selection for breast MR and/or breast MR biopsy resulting in fewer negative breast MR biopsies.

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Perioperative Breast MRI Is Not Associated with Lower Local Recurrence Rates in Ductal Carcinoma *In Situ* Patients Treated With or Without Radiation

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Introduction Perioperative MRI is frequently obtained in women with breast cancer; however, studies have not shown decreased rates of re-excision, and some report unnecessary increases in mastectomy rates. We examined local recurrence rates among women with ductal carcinoma in situ (DCIS) who underwent perioperative MRI as compared to those who did not. Methods All women who underwent breast-conserving surgery for DCIS in 1997-2010 were included from a prospectively maintained database. Patient characteristics and rates of ipsilateral breast tumor recurrence (IBTR) were compared in women with and without an MRI. Univariate and multivariate analysis were performed. Multivariate analysis was repeated in the subset of women who did not receive radiation (RT). Results A total of 2322 cases were identified; 596 had MRI and 1726 did not. Women who had MRI were younger and more likely to have a family history of breast cancer, have a clinical presentation, receive RT and endocrine therapy, be treated in later years, and had fewer close margins. At median follow-up of 62 months there were 184 IBTRs; 5-year IBTR rates were 8.5% (MRI) and 7.2% (no MRI) (p=0.52), and 10-year rates were 16.7% and 13.0%, respectively. On univariate analysis, IBTR was significantly associated with younger age, pre/peri-menopausal status, no RT, no endocrine therapy, and close margins. On multivariate analysis (Table 1), age, RT, endocrine therapy, and margin status all remained significant predictors of IBTR. MRI

was not associated with fewer IBTR (HR, 1.16; 95% CI, 0.77-1.73, p=0.48) after adjustment for all factors associated on univariate analysis with either undergoing MRI or risk of IBTR. Multivariate analysis of 878 women with no RT, controlling for these same variables, also showed that perioperative MRI was not associated with lower IBTR rates in this subgroup of patients (HR, 1.34; 95% CI, 0.77-2.35; p=0.30). Conclusions We observed no association between perioperative MRI and IBTR rate for patients with DCIS, even when RT was not given. The benefit of perioperative MRI for DCIS remains uncertain.

Table 1. Multivariate analysis for IBTR outcome

	N	IBTRs	Hazard ratio	95% confidence interval	p-value
AGE, per year	2255	182	0.977	0.964-0.990	0.0006
FAMILY HISTORY					
No	1367	106	1.0		
Yes	888	76	1.12	0.83-1.51	0.45
PRESENTATION					
Radiologic	2055	159	1.0		
Clinical	200	23	1.14	0.74-1.78	0.55
NUMBER OF EXCISIONS					
≤ 2	2066	162	1.0		
≥ 3	189	20	1.35	0.84-2.18	0.22
MARGINS					
Negative (> 2mm)	1880	136	1.0		
Close (≤ 2mm)	298	40	2.01	1.39-2.90	0.0008
Positive	77	6	1.43	0.62-3.27	
MRI					
Yes	582	37	1.16	0.77-1.73	0.48
No	1673	145	1.0		
RADIATION					
Yes	1377	79	1.0		
No	878	103	2.09	1.54-2.84	<0.0001
ENDOCRINE THERAPY					
Yes	534	27	1.0		
No	1721	155	1.98	1.31-2.98	0.0012
YEAR OF SURGERY					
1997-2003	972	129	1.0		
2004-2010	1283	53	0.86	0.59-1.26	0.43

IBTR, ipsilateral breast tumor recurrence

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Use of Metformin Correlates with Histological Type of Invasive Breast Carcinoma N. Besic,[1]* R. Petric,[1] B. Gazic,[1] N. Satej,[2] A. Perhavec.[1] *1. Surgical Oncology, Institute of Oncology, Ljubljana, Slovenia; 2. Community Health Centre Ljubljana, Ljubljana, Slovenia.*

Introduction: Metformin may exhibit inhibitory effects on cancer cells by inhibiting mTOR signaling pathway. Retrospective data have shown that patients with diabetes mellitus (DM) and breast cancer (BC) receiving metformin and neoadjuvant chemotherapy (NChT) had a higher pathological complete response rate than do diabetics not receiving metformin. But complete pathological response after NChT is less often in lobular carcinoma than in ductal carcinoma. The aim of our study was to find out if the patients with BC and DM receiving metformin have different tumor type of BC in comparison to diabetics not receiving metformin and non-diabetics. Methods: A retrospective chart review of 252 patients (mean age 66.6; range 38-93 years) with invasive BC and DM was performed; 126 patients were on metformin, while 126 patients were not receiving metformin. They were surgically treated at our institute from 2005-2011. Control group consisted of 316 consecutive patients with invasive BC without DM (mean age 59, range 28-86 y.), who were surgically treated our institute in 2006. Data on clinical and histopathology factors were collected. Statistical analysis of these factors (i.e. comparison of metformin group vs. no metformin DM group vs. controls) was performed by contingence tables and ANOVA. Results: Patients with DM not receiving metformin and patients with DM on metformin were older than patients without DM (68 vs. 65 vs. 59 years; p<0.001), had larger mean BMI (29 vs. 30 vs. 26.3; p<0.001), larger mean tumor diameter (2.8 vs. 2.6 vs. 2.4 cm; p<0.01) and higher tumor stage (pT3 or pT4: 26% vs. 16% vs. 13%; p<0.001). Patients on metformin had higher rate of ductal carcinoma than control group and patients with DM who were not receiving metformin (92% vs. 85% vs. 81%; p<0.05). Higher proportion of DM patients without and on metformin had hormone positive tumor in comparison to control group (91% vs. 90% vs. 82%; p<0.001). Conclusions: Patients on metformin had higher proportion of ductal carcinoma than patients with BC not receiving metformin. This may cause higher pathological complete response rate after NChT in diabetics on metformin in comparison to those not receiving metformin.

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Disconcordance Between Number of Scintigraphic and Peroperatively Identified Sentinel Lymph Nodes and Axillary Tumour Recurrence J. Volders,[1]* R. Van la Parra,[1] C. Bavelaar,[1] P. Barneveld,[2] K. Bosscha,[2] M. Ernst,[2] W. De Roos.[1] *1. Surgery, Gelderse Vallei Hospital, Ede, Netherlands; 2. Jeroen Bosch Hospital, Den Bosch, Netherlands.*

Introduction. In breast cancer patients sentinel node biopsy is considered a reliable method to establish the tumor status of the axilla. Periareolar, a radio active tracer is intradermally injected to identify the sentinel nodes preoperatively by scintigraphy. In addition, during surgery, patent blue dye is also injected to facilitate visual identification of the sentinel node. In a considerable number of patients there is a discrepancy between the number of scintigraphically identified sentinel nodes and the number of nodes identified during surgery. We hypothesized that the inability to find all the nodes peroperatively, that have been found by scintigraphy, might lead to an increase in the axillary recurrence rate. Methods. From a prospectively collected database patients who underwent sentinel node biopsy between January 2000 and July 2010 were identified. The number of scintigraphically and peroperatively identified sentinel nodes were compared . The axillary recurrences were scored. Patients were divided in 3 groups: group 1, scintigraphically more nodes identified than during surgery; group 2, more nodes identified during surgery than scintigraphically; group 3, similar number of nodes identified scintigraphically and during surgery. Results. Our population consisted of 1370 patients who underwent a SLN biopsy. Median follow up was 58.5 months (range 12-157). In 139 patients (10.1%) the number of radioactive nodes found during surgery was less than preoperative scanning and in 26.4% there were more peroperative nodes identified than seen scintigraphically. In group 1, 0/139 patients (0%) developed an axillary recurrence. In group 2 and 3 this was 2.7% (10/361) and 2.1% (18/870), respectively. No significant difference was found between the three groups regarding sentinel node status or distant metastasis. A higher number of scintigraphically identified nodes compared to the number of nodes identified during surgery did not lead to an increase in axillary recurrence rate. Conclusion. Axillary recurrence rate is not influenced by peroperatively non-identified sentinel nodes that were identified scintigraphically.

Table 1. Correlation between the number of identified sentinel nodes and axillary recurrence rate.

N=1370	Scintigraphically > peroperative	Peroperative> scintigraphically	Scintigraphically = peroperative
Sentinel node status - Negative - Positive - Failure	87 (62.6%) 43 (30.9%) 9 (6.5%)	241 (66.8%) 120 (33.2%) 0 (0.0%)	601 (69.1%) 238 (27.1%) 33 (3.8%)
Axillary recurrence	0 (0.0%)	10 (2.7%)	18 (2.1%)
Distant metastasis	9 (6.5%)	28 (7.8%)	96 (11.0%)

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Development of Rapid Diagnosis of Breast Cancer by using Intraoperative Novel Fluorescent Probe (glu-HMRG) to Visualize Cancer Cells H. Ueo,[1]* Y. Takahashi,[1] G. Sawada,[1] M. Ishibashi,[1] T. Matsumura,[1] R. Uchi,[1] K. Mima,[1] J. Kurashige,[1] Y. Takano,[1] Y. Kai,[1] T. Tobo,[3] A. Gamachi,[4] K. Shibuta,[6] H. Ueo,[6] Y. Maehara,[5] Y. Urano,[2] K. Mimori.[1] *1. Kyushu University Beppu Hospital, Beppu, Japan; 2. Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan; 3. Department of pathology, Kyushu University Beppu Hospital, Beppu, Japan; 4. Department of pathology, Almeida Memorial Hospital, Oita, Japan; 5. Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 6. Ueo breast clinic, Oita, Japan.*

Introduction: It is important to establish an intraoperative method to visualize cancer cell precisely in a short period of time in a state of “alive”. We explored the fluorescence probe (liquid reagent) to react γ-glutamyltranspeptidase (GGT) (Sci Transl Med 2011), which is specifically highly expressed in the cell membrane of malignant tumors and is a marker for visualization of cancer cells. We examined clinical significance of the current probe as an intraoperative diagnostic marker of the mammary gland stump and lymph nodes metastasis instead of pathological diagnosis. METHODS: From June to August

in 2012, breast cancer patients who underwent surgery were considered for eligibility. We applied 35 cases of invasive ductal cancer and two cases of non-invasive cancer. There were two recurrent cases, one was a liver metastasis and the other was a subcutaneous recurrence. We have 4 cases of benign mammary tumor. One hundred and thirty one lymph nodes were removed and examined in 33 cases. Metastatic lymph nodes were observed in 31 nodes. After splitting the excised tumors, the fluorescent probe reagent was sprayed onto the surface of them. Then, we applied the blue light (450-500 nm) from portable devices and measured the fluorescent intensity of cancer and non-cancerous area. RESULTS: 1) The incidence of positive intensity in invasive cancer, non invasive cancer, subcutaneous recurrent tumor, and the metastatic liver tumor were 35/39 cases (87%), 2/2 cases (100%), 1/1 case (100%) and 1/1 case (100%), respectively. 2) The positive fluorescent rate of the metastasis lymph nodes were 26/31 nodes (84%). Each presence of breast cancer cells detected by fluorescence probe was confirmed by pathological microscopic examination. CONCLUSION: We convinced the practical clinical usefulness of the novel fluorescence probe for breast cancer operation. It is useful to evaluate the presence of intraoperative residual cancer cells in mammary gland stump and lymph node metastasis especially facing at the partial resection and at the sentinel lymph node biopsy.

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The Impact of Oncoplastic Breast Surgery on Radiation Boost in Breast Conserving Therapy L.J. Strobbe,[1]* T. Van der Horst,[1] M. Keemers,[1] F. Van den Wildenberg,[1] F. Polat,[1] D.A. Schinagl.[2] *1. surgical oncology, CWZ, Nijmegen, Netherlands; 2. Radboud UMC, Nijmegen, Netherlands.*

Background: The integration of wide local tumour resection and reconstruction of the breast following plastic surgical principles is called oncoplastic surgery (OPS). Since the resection volumes in OPS are believed to be larger, the resulting scars will be more complex leading to larger boost volumes. The objective of this study is to quantify the effect of the resection volumes on the boost volume in OPS. Methods: We retrospectively reviewed 37 consecutive patients (2009), treated with classic breast conserving surgery (BCS) with free margins and compared them with 37 consecutive patients (2009 – 2010), treated with OPS. The studied items were tumour type, involved breast quadrant, tumour size on imaging, pathologic size, resection volume, resection margin, whole breast radiation volume (WBRV) and the boost radiation volume administered. The operative technique in "standard BCS" consisted of wide local excision without closure of the glandular defect. OPS consisted of predefined resections with closure of the defect using glandular flaps. Radiotherapy planning was CT simulation-based in relation to the position of the clips and in the framework of multidisciplinary consultation. Results: In the OPS group more patients with DCIS were operated, making this group more at risk for positive margins. In the OPS group more resections were performed in cosmetically difficult regions (medially and caudad). Mean tumour size was 13.4mm (BCS) vs 15.8mm (OPS) (p=0.074). Mean resected volume was larger in OPS: 170ml vs 115ml (p=0.013). Surgical margins were with 3,5mm comparable, because mostly measured relative to the skin or the pectoral fascia. Mean WBRV seemed larger in BCS, but not statistically significant: 830.53ml vs 594.03ml (p=0.119). The boost volume was comparable with 92.01ml (BCS) vs 88.29ml (OPS) (p=0.42).Closure of the glandular defect and close communication between surgeon and radiotherapist results in similar boost volumes, irrespective of the resected volume. In conclusion, OPS succeeds in local resection of larger tumours with comparable margins. This does not translate into larger boost volumes, compromising the cosmetic outcome of OPS.

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Incidence of Inflammatory Breast Cancer in Women, 1992-2009, United States B.S. Goldner,[1]* C. Behrendt,[1] B. Lee,[2] S.L. Chen.[1] *1. City of Hope Medical Center, Duarte, CA; 2. Harbor-UCLA Medical Center, Torrance, CA.*

Introduction: A prior report suggested that the annual incidence of inflammatory breast cancer (IBC) increased in the United States during the period from 1988 through 2000. We hypothesized that IBC incidence has continued to increase through 2009, possibly more so among women in younger age groups. Methods: We queried the Surveillance Epidemiology and End Results (SEER) database for all cases of IBC in women age 20 years and older between the years of 1992 and 2009. Cases were defined as breast tumors with at least one of the following codes: extent of disease size-998, extension-70, or ICD-3-O morphology 8530/3. Age-adjusted incidence (standardized against the 2000 U.S. population) was examined by year, age, and race. Results: During 1992-2009, annual incidence of IBC averaged 2.1 (95% CI 2.1-2.2) cases per 100,000 U.S. women. Incidence did not increase over time in any 5-year age group. It also did not vary significantly from year to year except between 2003 and 2004, when there was a jump (from 1.6 (1.4-1.8) to 3.1 (2.8-3.4) cases per 100,000), which returned to previous levels thereafter. That one-time jump occurred in all age and racial groups. Overall, incidence rose steeply with age until reaching a plateau at age 70. In addition, incidence was significantly lower for Asian (1.4, 1.3-1.6) than for White (2.1, 2.1-2.2) or Black (3.0, 2.8-3.2) women. Conclusion: Contrary to prior report, overall and age-specific incidences of IBC have remained stable for nearly 2 decades. An apparent jump in incidence between 2003 and 2004 was transient and affected all age and racial groups, suggesting that it was administrative in nature. Despite being described often as a disease of younger women, IBC disproportionately affects older women. We find that the incidence of this disease is lowest among Asian women and highest among Black women, suggesting that the pathogenesis of IBC is affected by one or more factors that vary by race, such as age of menarche, body mass index, diet or other lifestyle factors.

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Uptake and Experiences of Breast Cancer Patients Referred for Fertility Preservation J.D. Lewis,[1]* C. Silva,[2] G.P. Quinn,[3] M.C. Lee.[3] *1. University of Cincinnati College of Medicine, Cincinnati, OH; 2. University of South Florida, Tampa, FL; 3. H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.*

Introduction: The 2006 ASCO guidelines suggest women of childbearing age receive counseling and referrals regarding the impact of cancer treatment on fertility. Less is known about the uptake of fertility preservation (FP) among these women. The objective of this study was to evaluate the experiences of patients referred for FP from a multidisciplinary breast cancer program. Methods: After IRB approval, patients diagnosed with a primary breast cancer between January 2006 and June 2011 and referred for FP counseling were identified via queries of institutional databases. Basic demographics, clinicopathologic, treatment, and outcome data were collected. Patients who received a consultation with a reproductive endocrinologist (REI) and did not pursue FP were contacted via telephone for a follow-up survey. Results: Twenty-two patients had a consultation with a REI. Fifteen saw a REI prior to any treatment, 5 after surgery but prior to systemic therapy, 1 after systemic therapy, and 1 at an unknown point during treatment. Most women (41%) underwent consultation with both surgical and medical oncology prior to REI consult. Thirteen (59%) chose embryo or oocyte preservation. Of the remaining 9, 7 (78%) responded to a telephone survey. Six (86%) recalled counseling at the initial visit or prior to chemotherapy; 1 did not. Barriers to FP included: cost (3), perceived delay in chemotherapy (2), being overwhelmed by cancer diagnosis (2), uncertainty of FP effects on cancer (1), and ethical concerns (1). Patients who pursued FP had fewer children on average at time of referral than those who did not pursue FP. The majority (61.5%) of those who pursued FP were given anthracycline-based chemotherapy while 77.8% of those who did not pursue FP were given taxane-based or no chemotherapy. Conclusions: Women with children and those undergoing taxane-based chemotherapy were less likely to pursue FP; however, other barriers were cited by these women. Patients counseled by multiple oncology providers in a multidisciplinary setting prior to REI consultation were more likely to pursue FP. Consultation with multiple oncology specialists may enhance decision-making regarding FP.

At time of FP Referral	All Cases n=22	Pursued FP n=13	Did Not Pursue FP n=9
Mean age, years (range)	32.5 (22.8-43.8)	31.5 (24.3-43.8)	34 (22.8-41.7)
Mean parity (range)	0.5 (0-2)	0.3 (0-2)	0.8 (0-2)
Median parity	0	0	1
Nodal involvement	12 (54.5%)	6 (46.2%)	6 (66.7%)
Known distant metastases	0	0	0
Cancer specialist seen prior to REI consult			
Surgical only	10 (46%)	3 (23%)	7 (78%)
Medical only	0	0	0
Both	9 (41%)	7 (54%)	2 (22%)
Unknown	3 (14%)	3 (23%)	0
Chemotherapy recommended	21 (96%)	13 (100%)	8 (89%)
Anthracycline-based	11 (52.4%)	8 (61.5%)	2 (25%)
Taxane-based	10 (47.6%)	5 (38.5%)	6 (75%)
Endocrine therapy recommended	10 (46%)	6 (46%)	4 (44%)

P79

HER3 Expression in Ductal Carcinoma *In Situ* Strongly Correlates with Tumor Grade and is Independent of Tumor Phenotype

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Introduction: HER3, a member of the human epidermal growth factor receptor (EGFR) family when coupled with HER2 as a heterodimer, is known to possess potent mitogenic capabilities, promotes invasion and confers resistance to targeted therapies against HER2 and EGFR. Although the prognostic implications of HER3 expression in invasive breast cancer (BC) have been reported, little is known regarding its role and expression in early BC. We evaluated HER3 expression in DCIS patients (pts) and its relationship to tumor grade and hormone receptor statuses. Methods: IHC was performed using HER3 antibody on paraffin-embedded tissue containing DCIS only from 91 pts diagnosed with DCIS from 2003-2012 at a single institution. Cytoplasmic HER3 expression was evaluated by a single pathologist to reduce interpretative variability. HER3 expression was calculated by multiplying the intensity (1-3) by the percentage of DCIS stained (0-100%) to yield an overall score ranging from 0 to 300. Results: Cytoplasmic HER3 expression was found in 88/91 (96.7%) of DCIS pts (mean±SE 147.1±8.2). All slides with positive expression showed little to no background HER3 staining. There was a significant positive correlation between HER3 expression and grade (mean±SE 79.5±19.6, 137.4±12.0 and 170.6±11.5 for grades 1, 2 and 3, p=0.001). There was no association between HER3 and either Luminal A (p=0.14) or Luminal B phenotype (p=0.33) or HER2 status (p=0.21). Triple negative (ER-/PR-/HER2-) pts (n=6) had greater HER3 expression compared to all others (202.2±25.7 vs 143.8±8.6) but it did not reach statistical significance (p=0.08). Interestingly, all 6 triple negative pts showed ≥ 2+ intensity on staining with 100% positive staining of all the DCIS foci. Conclusion: In DCIS, greater cytoplasmic expression of HER3 is strongly correlated with higher nuclear grade. Since local tumor recurrence is associated with high grade DCIS, the increased HER3 expression may serve as a useful target, independent of tumor phenotype, to eliminate disease or prevent recurrence in this group. Triple negative DCIS exhibited greater HER3 expression, but confirmation is needed in additional pts.

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Trend Toward Increasing Utilization of Radiation in Malignant Phyllodes Tumors: An Analysis of Over 3200 Patients from 1998 to 2009

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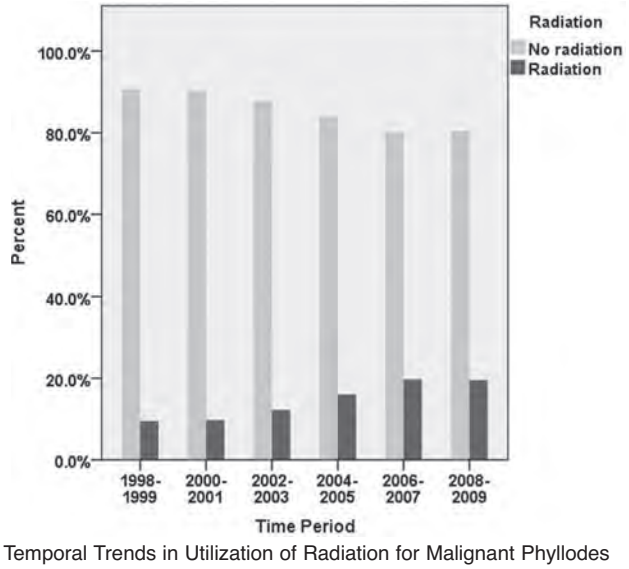
Introduction: Malignant phyllodes tumors of the breast are uncommon. Currently, there are no standard treatment guidelines for adjuvant therapy. We hypothesized that there has been a trend towards increased use of radiation despite its uncertain effect on outcomes. Methods: Using the National Cancer Data Base, treatment trends and predictors of radiation utilization were examined for women with malignant phyllodes from 1998 to 2009. Kaplan-Meier and Cox regression were used to determine the effect of radiation on local recurrence (LR), disease-free survival (DFS), and overall survival (OS). Results: Of 3,210 patients, 57% underwent lumpectomy and 43% underwent mastectomy. Overall, 14.3% received radiation, with utilization doubling over the study period (9.5% in 1998-1999 vs. 19.5% in 2008-2009, p<0.001, see Figure). Women were significantly more likely to receive radiation if they were diagnosed later in the study (OR 2.00, 95% CI 1.13-3.54), were age 50-59 (OR 1.73, 95% CI 1.18-2.52), had tumors >10cm (OR 2.39, 95% CI 1.63-3.50), or had nodes removed (OR 2.00, 95% CI 1.52-2.63). Race/ethnicity, socioeconomic factors, hospital characteristics, type of surgery, and margin status were not independent predictors of radiation. Of 1,774 patients with known recurrence status, overall recurrence was 14.1% and LR was 5.9%. With 53 months median follow-up and controlling for potential confounders, radiation reduced LR (aHR 0.43, 95% CI 0.19-0.95) but had no impact on DFS or OS. Conclusions: Use of adjuvant radiation for malignant phyllodes doubled from 1998 to 2009. Tumor factors and time were the main determinants of utilization. Radiation decreased LR but had no effect on DFS or OS.



Temporal Trends in Utilization of Radiation for Malignant Phyllodes

P81

Characteristics of Patients with Small Breast Tumors and Axillary Lymph Node Metastases

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Introduction: The presence of axillary lymph node (ALN) metastasis is the strongest prognostic factor for women with invasive breast cancer. Our previously presented work (SSO, 2012) demonstrated that lymphovascular invasion (LVI) and tumor size were strongly predictive of ALN metastasis. Our current goal is to examine the characteristics of an independent sample of patients to see if there are unique predictors of nodal metastases in patients with small tumors. Methods: A retrospective, case-controlled study was performed on subjects with invasive breast cancer from 2001-2012 who had tumors 10 mm or less, underwent ALN sampling, and did not receive neoadjuvant chemotherapy. There were fifty women with node positive tumors and these were matched by tumor size and age with 100 women who had node negative tumors. Data were collected on tumor type, grade, LVI, multifocal/multicentric (MFC) tumors, hormone receptors, menopausal status, personal and family history of breast cancer, and personal and family history of ovarian cancer. Univariate and multivariate logistic regression were used to identify factors associated with ALN metastases. Results: Factors associated with ALN metastases in small tumors on univariate and multivariate analysis ($p<0.05$) were LVI ($p<.0001$), MFC tumors ($p<.0001$), and family history of breast cancer ($p=.0003$). Conclusions: As expected, LVI and MFC tumors were significant predictors of ALN metastases in patients with small tumors. An unusual finding was that family history also appeared as a significant predictor. Further studies are needed to develop more detailed determinants for this underrepresented population of patients with small tumors and positive nodes. These efforts may ultimately lead to a better understanding of their unique tumor biology and may have significant treatment implications. "The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army (DOA), Department of the Navy (DON), Department of Defense (DOD), or US Government."

P82

Breast Magnetic Resonance Imaging (MRI) is a Sensitive but Non-specific Means to Assess Primary Tumor Response to Neoadjuvant Chemotherapy

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Introduction: Neoadjuvant chemotherapy (NAC) is often employed for operable/advanced breast cancer patients to permit breast conservation surgery. The ability of either magnetic resonance imaging (MRI) or mammography to predict pathologic response of the primary tumor is poorly documented and limited. This study sought to evaluate the ability of post NAC MRI to predict pathological tumor response. Methods: 56 patients underwent MRI following NAC (Anthracycline/Taxane/Trastuzumab-based)

(2009-2012). 33 patients also underwent mammography. All patients underwent either lumpectomy or total mastectomy with axillary lymph node evaluation. MRI and mammographic response, molecular subtype (ER/PR and HER 2 neu status) and histopathology of the primary tumor was abstracted. Standard statistical analysis was performed. Results: Median patient age was 39 years. A significant correlation between post-NAC breast MRI and post-NAC primary breast tumor pathological response (p = 0.018) was noted. The sensitivity of the post-NAC MRI and mammography to predict complete versus partial tumor primary tumor response was 65% and 30%, the specificities were 69% and 78%, the positive predictive value (PPV) was 48% and 38%, and the negative predictive values were 82% and 72% respectively. No statistical significance between breast MRI and mammography, tumor histology or molecular subtype was appreciated (Table 1). Conclusion: Although MRI was superior to mammography for predicting a complete pathological response of the breast tumor following NAC, the poor specificity of MRI relative to mammography implies it is a poor surrogate for decision making in regards to ideal surgical therapy after NAC. No correlation between MRI response and tumor molecular subtypes was identified, but this study is limited by small sample size and additional research is warranted.

Comparison of Magnetic Resonance Imaging Partial and Complete Primary Breast Tumor Response in Patients After Receiving Neoadjuvant Chemotherapy.

	MRI partial response following NAC (N = 33)	MRI complete response following NAC (N = 23)	p value*
Tumor characteristics on affected side:			p = 0.613
Histology			
Invasive ductal carcinoma	29 (59%)	20 (41%)	
Invasive lobular carcinoma	4 (57%)	3 (43%)	
Pathology Response			p = 0.018
Complete	6 (35%)	11 (65%)	
Partial	27 (69%)	12 (31%)	
Mammographic Complete Response (N = 33)			p = 0.164
Yes	4 (50%)	4 (50%)	
No	19 (76%)	6 (24%)	
Stage Prior to NAC			p = 0.714
2A	3 (50%)	3 (50%)	
2B	10 (56%)	8 (44%)	
3A	11 (65%)	6 (35%)	
3B	9 (64%)	5 (36%)	
3C	0 (0%)	1 (100%)	
Molecular Subtype			p = 0.154
ER+ PR+ HER2- (Luminal A)	6 (40%)	9 (60%)	
ER+ PR+ HER2+ (Luminal B)	17 (71%)	7 (29%)	
ER- PR- HER2- (Triple negative)	6 (75%)	2 (25%)	
ER- PR- HER2+ (HER2 overexpression)	4 (44%)	5 (56%)	

Abbreviations: MRI, Magnetic resonance imaging; NAC, Neoadjuvant chemotherapy; N, number of patients; ER, Estrogen Receptor; PR, Progesterone Receptor, HER 2, Human Epidermal Growth Factor Receptor 2, * p value statistically significant <0.05, for the trend

P83

Demographic Influences in Breast Reconstruction after Oncologic Surgery in the State of Florida H.M. King,[1]* T. Koru-Sengul,[2] F. Miao,[3] M. Byrne,[2] D. Franceschi,[1] E. Avisar.[1] *1. Department of Surgery, University of Miami Miller School of Medicine, Miami, FL; 2. University of Miami Miller School of Medicine, Department of Epidemiology and Public Health, Miami, FL; 3. Sylvester Comprehensive Cancer Center, Miami, FL.*

Background: Multiple studies have attempted to discern factors influencing reconstruction after surgery for breast cancer. We sought to investigate factors that may affect reconstruction rates in Florida. Methods: A database linking the Florida Cancer Data System (FCDS) to the Agency for Health Care Administration (AHCA) and US Census identified patients who received surgery for breast cancer over a ten year period. ICD–9 codes indicated oncologic and plastic surgical procedures performed. Differences in reconstruction rates were compared for characteristics such as race, ethnicity, marital status, type of medical institution, insurance status and socioeconomic status (SES). Smoking status was included as this can alter reconstructive options. Results: Between 1996 and 2007, 95201 patients had breast cancer surgery. 91% of surgical patients were white, 9% black, and 1% were considered other race. Reconstructive surgery was performed in 14812 (16%), of which 7% had lumpectomy and 25% mastectomy. Only 12% of black surgical patients had reconstruction versus 16% white and 25% other race (p<0.0001). Of black reconstructed patients, 66% had flap procedures versus 20% in whites. There was a trend of increasing reconstruction rates with higher SES (low SES=11%, high SES=21%). 20% or greater insured patients (private, military or other) were reconstructed versus 5% of Medicare, 12% of Medicaid and 13% of uninsured. 95% of surgical patients were urban dwellers and 16% had reconstruction compared to 11% of rural dwellers. Only 10% of patients had surgery at teaching hospitals, 22% were reconstructed versus 15% of surgical patients at non-teaching institutions. Reconstruction rates were higher at high volume versus low volume centers (24% versus 14%). Smoking status did not alter reconstruction but marital status was influential (never married/married=18%, versus divorced/widowed=10%). Conclusion: Breast reconstruction was performed in a very low number of patients. Black race, low SES and public or no insurance were associated with lower reconstruction rates. Higher rates were noted in urban dwellers, high volume and teaching centers.

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Monitoring Soluble HER2 Extracellular Domain in the Serum of Breast Cancer Patients Using a Refined ELISA Assay C. Edwards,[3]* B. Ky,[2] J.C. Tchou,[3] H. Zhang.[1] *1. Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 2. Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 3. Division of Surgical Oncology, Rena Rowan Breast Center, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.*

Introduction Overexpression of the HER2/neu receptor, which occurs in 15-30 percent of breast tumors, is linked to poorer prognosis and responsiveness to trastuzumab. It has been hypothesized that serum levels of HER2/neu could be used to monitor the course of disease in breast cancer patients, particularly to detect recurrence or metastasis before it is clinically evident. However, existing data on the clinical applicability of serum HER2/neu levels are mixed, perhaps because of the lack of a standardized assay. We hypothesized that using an ELISA assay implementing a novel buffer, MBB, known to reduce interference from serum antibodies, would lead to more accurate measurement of serum HER2/neu, potentially increasing clinical relevance of this biomarker. Methods Informed consent was obtained from 56 women with breast cancer. We collected serum samples every one to two months. Samples were collected just prior to surgery in a subset of patients. Levels of soluble HER2/neu extracellular domain were measured in each sample using our refined ELISA assay. Each patient received standard of care treatment for her breast cancer. Tumor characteristics and patient outcome data were obtained by chart review. Results Pre-treatment (e.g. surgery, radiation, or chemotherapy) samples were available from 12 patients, of which six patients had HER2/neu overexpressing tumors. These patients had higher serum levels than patients with tumors without HER2/neu overexpression (p=0.02). Of three patients who had recurrence or metastasis, HER2/neu level contemporaneously significantly increased from baseline. Of three patients in which HER-2/neu values were elevated before surgery and post-surgery values were available, two had a significant decrease in HER-2/neu level after surgery (p<0.05). Conclusions These pilot data show that HER-2/neu level, as measured by an ELISA assay implementing MBB buffer, appears to increase with progression of disease. There was a trend towards decrease in HER-2/neu level after breast cancer surgery. Our study is ongoing, but preliminary results show that this assay has promising utility in monitoring disease in women with breast cancer.

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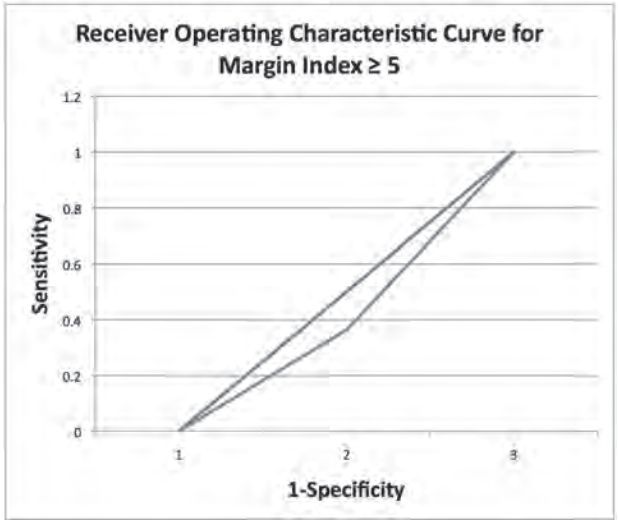
Comparing Margin Diameter and Margin Index in Predicting Residual Disease Following Partial Mastectomy A. Widmyer,[2] D.F. Barnas,[1]* A.D. Bleznak,[3] H. Chung,[2] E. Dellers.[2] *1. Surgery, Borgess Medical Center, Kalamazoo, MI; 2. Lehigh Valley Health Network, Allentown, PA; 3. Eastern Virginia Medical School, Norfolk, VA.*

A significant predictor of local recurrence after breast conservation is surgical margin status, but there continues to be a lack of agreement as to the optimal margin distance. A recent study by Margenthaler asserted that margin index

was a better predictor of residual disease than margin diameter alone. We applied this tool to our patients to determine if margin index would be a better predictor of re-excision status. We performed a retrospective analysis of 217 patients undergoing breast conserving surgery in 2009 and 2010. Of those 217 patients, 95 underwent re-excision for close or positive margins. 88 of those patients had the requisite data elements to be included in our study. Of those patients, 41 had re-excision for close margins. Margin index was then calculated as: margin index = {closest margin (mm)/ tumor size (mm)} x 100, with index ≥ 5 being optimal as described in the original study. A receiver operating characteristic (ROC) curve was then calculated for a margin index ≥ 5. The median age of the 41 patients in our study was 55 years of age. All patients had Stage I or II disease with a median tumor size of 2.0 cm. Our mean margin distance was 0.91 mm; 28 patients (68%) had a margin < 1 mm, 7 (17%) had a margin of 1-2 mm, and 6 (15%) had a margin > 2 mm. Eight patients had residual disease; 6 had a margin distance of < 1 mm (75%), 1 had 1-2 mm (12.5%), and 1 > 2 mm (12.5%). The mean margin index was 2.78. 25 of the 41 (60%) patients had a margin index of ≥ 5. Of the 8 of 41 (19.5%) patients with residual disease on re-excision, 4 had a margin index ≥ 5 and 4 had a margin index of < 5. This resulted in a sensitivity of 50% and a specificity of 63.6% for the margin index. The ROC curve was plotted with an area under the curve of 0.568 see figure 1. In our study population, margin index ≥ 5 did not prove to be a better predictor of residual disease. Our study was limited by selection bias, its retrospective nature, and a small number of patients, particularly those with < 1mm margin. Further investigation will be needed to find a more reliable predictor of residual disease; until then, we recommend utilizing margin diameter.

Figure 1



P86

A Proposed Scale for Severity of Mastectomy Skin Necrosis Correlates with Need for Intervention A.C. Degnim,[1]* T. Hoskin,[2] D.R. Farley,[1] C.S. Grant,[1] J.C. Boughey,[1] S. Jacobson,[1] T.A. Torstenson,[1] R.D. Reusche,[1] V. Lemaine.[1] *1. Mayo Clinic Department of Surgery, Rochester, MN; 2. Mayo Clinic Biomedical Statistics and Informatics, Rochester, MN.*

Introduction: With increasing use of immediate breast reconstruction after mastectomy, skin flap necrosis is a problem that deserves further study. We propose a new scale to describe and discriminate severity and extent of mastectomy skin necrosis. Methods: Women who underwent skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) with immediate breast reconstruction from Nov 2009 to Oct 2010 were studied retrospectively. Surgeons screened all patient records to find cases with any concern of skin ischemia or necrosis within 90 days of operation. These cases were reviewed (records and available photographs) by a workgroup of breast surgeons and plastic surgeons. Photographs were scored for necrosis severity, assigning a letter score on a four-point scale for depth of necrosis and a numerical score on a four-point scale for the area. Necrosis severity scores were evaluated for correlation with need for surgical intervention. Results: 177 patients underwent 299 procedures (204 SSM and 95 NSM); 69% of patients underwent bilateral procedures. Postoperatively, 233 breasts (77.9%) had no ischemic problems and 47 (15.7%) had mild ischemia/necrosis not needing intervention. Overall, 17 (9.6%) of patients and 19 (6.4%) of breasts had necrosis requiring reoperation. Of 238 breasts with a postoperative photograph within 60 days of surgery, 15 (6.3%) breasts required intervention (3.8% of SSM and 11.4% of NSM). Reoperations for necrosis occurred from 4 to 62 days (median 28) after mastectomy. Based on photograph scores, both the letter score (depth) and numerical score (area) individually, as well as their combinations, correlated with a need for additional surgical intervention per breast (see Table). The combined letter and numerical score demonstrated a c-statistic of 0.97 for SSM and 0.94 for NSM, for predicting need for additional intervention. Conclusions: A simple scoring system for the severity of mastectomy skin necrosis is proposed, incorporating the depth and area of skin necrosis. Scores obtained with this severity scale correlate strongly with the need for additional surgical intervention to treat mastectomy skin necrosis.

Necrosis scores and need for intervention after SSM or NSM in 238 breasts with postoperative photographs

Depth Score	N (%)	Needed Intervention N (%)	Area Score	N (%)	Needed Intervention N (%)
A: No concern of ischemia	167 (70.2)	0	1: None	167 (70.2)	0
B: Skin color change indicating ischemia	12 (5.0)	1 (8.3)	2: 1-10%	35 (14.7)	4 (11.4)
C: Partial thickness skin necrosis	30 (12.6)	2 (6.7)	3: 11-30%	16 (6.7)	4 (25.0)
D: Full thickness skin necrosis	29 (12.2)	12 (41.4)	4: >30%	20 (8.4)	7 (35.0)

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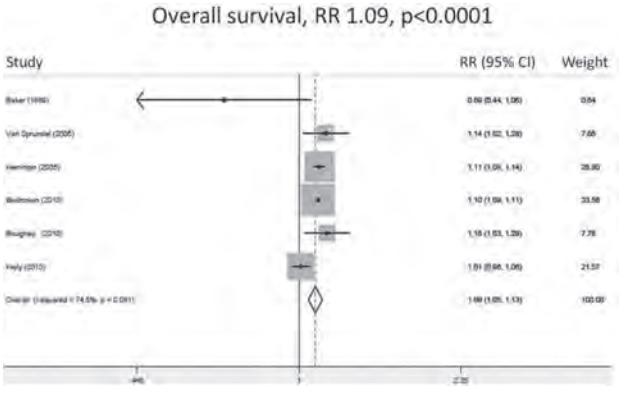
Contralateral Prophylactic Mastectomy after Unilateral Breast Cancer: A Systematic Review and Meta-Analysis O.M. Fayanju, C. Stoll, G.A. Colditz, J.A. Margenthaler.* *Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

Introduction Rates of contralateral prophylactic mastectomy (CPM) continue to increase despite limited prospective data and conflicting evidence of survival benefit. We present results of a systematic review and meta-analysis of CPM in women with unilateral breast cancer. Methods We searched 5 databases (Embase, PubMed, Scopus, ClinicalTrials.gov, & Cochrane) and the bibliographies of retrieved papers for articles reporting outcomes in CPM recipients with a history of unilateral primary breast cancer. Data were independently abstracted and cross-checked by two coders. We report pooled relative risks (RR) and 95% confidence intervals (CI) at 2-tailed $p<0.05$ significance from fixed- and random-effects meta-analyses and 2 stratified subanalyses, one based on study publication date (≤2008 vs. ≥2009) and one on patients' country of origin (United States [US] vs. non-US). Results Of 93 articles reviewed, 17 observational studies met eligibility criteria. Mean/median follow-up was ≥2 years for all 17 studies and ≥5 years for 13. CPM recipients had a 9% improvement in overall survival (OS; 6 studies; CPM n=10,287, no CPM n=143,055; RR=1.09 [95% CI 1.05-1.13, $p<0.0001$]), a 31% decrease in breast-cancer-specific mortality (BCM; 4 studies; CPM n=10,120, no CPM n=142,105; RR=0.69 [95% CI 0.56-0.85, $p=0.001$]), and a 36% decrease in distant/metastatic recurrence (DMR; 5 studies; CPM n=953, no CPM n=3323; RR=0.64 [95% CI 0.51-0.81, $p<0.001$]). CPM was associated with improved OS (RR 1.08, 95% CI 1.01-1.16, $p=0.04$) for patients in studies published in 2009 or later but not from earlier studies. CPM was associated with improved OS (RR 1.10, 95% CI 1.08-1.13, $p<0.001$) and decreased BCM (RR 0.70, 95% CI 0.57-0.87, $p=0.001$) for US-based patients only. CPM was associated with decreased rates of DMR regardless of publication date ($p<0.05$), but only US-based CPM recipients had decreased rates of DMR (RR 0.65, 95% CI 0.52-0.82, $p<0.001$). Conclusion Our review of CPM indicates a potential survival benefit for women with a history of unilateral breast cancer. Prospective trials are needed to confirm our findings and to elucidate international outcome differences following CPM.



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The Role of Radical Mastectomy in the Current Era J.D. Lewis,[1]* N. Khakpour,[2] C. Laronga,[2] J.V. Kiluk,[2] W. Sun,[2] M.C. Lee.[2] *1. University of Cincinnati College of Medicine, Cincinnati, OH; 2. H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.*

Introduction: Both early detection of and improved systemic therapies for breast cancer have nearly eliminated the need for radical mastectomy (RM). However, we hypothesized that RM may be performed with minimal morbidity in patients with chemo- and hormonal therapy resistant local-regional disease, who refuse systemic therapy, or who otherwise require extended surgery for local control. Methods: An IRB-approved retrospective review of women having RM was conducted. Indications included local control of either primary or recurrent disease. Data reviewed included clinicopathologic features, operative procedures, early complications, and survival. Results: From 2000-2011, 23 women underwent RM for initial (17 patients, 73.9%) or recurrent (6 patients, 26.1%) disease. Median age was 49.6 years (range 30.4-77.1); median length of hospitalization was 2 days (range 1-9). Fourteen (60.9%) were performed for primary surgical treatment, 9 (39.1%) as completion RM. Pathology included 18 (78.3%) invasive ductal carcinoma, 2 (8.7%) sarcoma, 2 (8.7%) metaplastic carcinoma, and 1 (4.3%) malignant phyllodes. Excluding 3 patients with metastases who did not return following discharge after surgery, median follow-up was 15.4 months (range 1.5-66). Nine (39.1%) patients had metastases at the time or within 30 days of surgery, 4 (17.4%) additional patients developed distant disease >30 days after surgery. Twelve (52.2%) had complaints of preoperative pain; 8 (66.7%) had interval improvement or resolution of pain following surgical resection. Preoperatively, 8 (34.8%) patients had wound problems and/or infections. Postoperatively, 6 (26.1%) patients experienced wound breakdown; 3 (13%) required debridement and skin grafting, 2 (8.7%) requiring readmission. Three (13%) patients developed locoregional recurrences. Estimated median survival for the entire group was 16.1 months. Estimated median survival for those who underwent RM for primary disease without metastases was at least 26.2 months; five (50%) are currently alive and disease free. Conclusions: Although excessively morbid for most patients, RM may be performed relatively safely for palliation or curative resection in well-selected patients.

Radical Mastectomy by Indication

	Initial Not Metastatic (N=10)	Recurrent Not Metastatic (N=4)	Metastatic Disease Within 30 Days of Surgery (7 Initial, 2 Recurrent) (N=9)	Total (N=23)
Median tumor size, cm (range)	9.6 (0.8-25)	3.6 (2.1-6.5)	7.8 (1.1-20)	7.8 (0.8-25)
Negative margins achieved	8 (80%)	0 (0%)	3 (33.3%)	11 (47.8%)
Mean estimated blood loss, ml (range)	275 (100-1000)	50 (50-550)	300 (100-2000)	250 (50-2000)
Mean units of blood transfused (range)	0 (0-2)	0 (0-0)	0 (0-4)	0 (0-4)
Primary closure, N (%)	3 (30%)	3 (75%)	2 (22.2%)	8 (34.8%)
Readmission within 90 days, N (%)	0 (0%)	1 (25%)	2 (22.2%)	3 (13%)
Return to operating room within 90 days, N (%)	1 (10%)	1 (25%)	1 (11.1%)	3 (13%)
Received radiation if recommended (rec), N/N rec (%)	8/10 (80%)	1/1 (100%)	1/1 (100%)	10/12 (83.3%)
Received chemotherapy if rec., N/N rec (%)	9/10 (90%)	2/2 (100%)	8/8 (100%)	19/20 (95%)
Estimated median survival, months	26.2	N/A	14	16.1

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Expression of Bcl2 and p53 as a Prognostic Factor in High Grade Infiltrating Duct Carcinoma of the Breast B. Chikman,[1] A. Kapiev,[1] R. Lavy,[1]* L. Habler,[2] J. Sandbank,[2] A. Halevy.[1] *1. Assaf Harofeh Medical center i, Tel Aviv, Israel; 2. Institute of Pathology assaf Harofeh Medical center, Tel Aviv, Israel.*

Background: p53 and bcl-2 are known as key regulators of apoptosis. Bcl2 expression was positively associated with favorable prognostic features and better survival, alterations in p53 are associated with poor prognosis in breast cancer. The possible relationship of bcl-2 and p53 expression with different biological type of breast cancer and their significance for prognosis in high grade breast cancer is not studied in depth. Methods: 126 patients with high grade infiltrating duct carcinoma (grade 3) without previous neo-adjuvant therapy were selected and served as the basis for this study. bcl-2 and p53 expression were studied immunohistochemically. bcl-2 and p53 expression was considered as positive in cases when more than 25% of tumor cells were stained. Results: 62/ 126 (49.2%) of patients were bcl2 positive and 57/126 (45.3%) of patients were p53 positive. Bcl2-positive tumors were associated with ER-positive and PR-positive tumors (p<0.0001), and oppositely p53-positive tumors were associated with ER-negative (p=0.035) and PR-negative tumors (p=0.021), 54% of triple negative tumors had strong had strong staining for p53, compared to 13-18% of such kind staining in other biological subtypes of tumors (p=0.003). Bcl2 overexpression was associated with better overall (p=0.012) and disease free survival (p=0.015), whereas p53 overexpression did not showed prognostic significance. Conclusion: p53 and bcl2 overexpression has very specific distribution according to biological type of the tumor, but the prognostic significance was observed only for Bcl2 overexpression.

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WITHDRAWN

P91

The Role of Magnetic Resonance Imaging in Assessing Residual Disease and Pathologic Complete Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy: A Systematic Review R. Schipper,[1]* M. Lobbes,[2] R. Prevos,[2] M. Smidt,[1] V. Tjan-Heijnen,[3] M. Van Goethem,[4] R. Beets-Tan,[2] J. Wildberger.[2] *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 Medical Oncology, Maastricht, Netherlands; 4. University Hospital Antwerpen, department of Radiology, Antwerpen, Belgium.*

Introduction: This systematic review aimed to assess the role of magnetic resonance imaging (MRI) in evaluating residual disease extent and the ability to detect pathologic complete response (pCR) after neoadjuvant chemotherapy for invasive breast cancer. Materials and methods - Pubmed, Cochrane library, Medline, and Embase databases were searched for relevant studies published until July 1, 2012. After primary selection, two reviewers independently assessed content of each eligible study using a standardized extraction form and pre-defined inclusion and exclusion criteria. Results - A total of 35 eligible studies were selected. Correlation coefficients of residual tumor size assessed by MRI and pathology were good, with a median value of 0.698. Reported sensitivity, specificity, positive predictive value, and negative predictive value for predicting pCR with MRI ranged from 25-100%, 50-97%, 47-73%, and 71-100%, respectively. Both overestimation and underestimation were observed. MRI proved more accurate in determining residual disease than physical examination, mammography, and ultrasound. Recent studies suggest that diagnostic accuracy of MRI after neoadjuvant chemotherapy might be influenced by treatment regimen and breast cancer subtype. Conclusion - Breast MRI accuracy for assessing residual disease after neoadjuvant chemotherapy is good and probably surpasses other diagnostic means. However, both overestimation and underestimation of residual disease extent can be observed.

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The Effects of Adding Preoperative Magnetic Resonance Imaging to Patients with Invasive Cancer Eligible for Breast Conserving Surgery: A Comparative Study A. Fancellu,[1]* D. Soro,[2] P. Castiglia,[3] V. Marras,[4] M. Melis,[5] P. Cottu,[1] S. Mulas,[1] A. Cherchi,[1] C. Pusceddu,[6] L. Simbula,[2] G. Meloni.[2] *1. University of Sassari - Dept. of General Surgery - Clinica Chirurgica, Sassari, Italy; 2. University of Sassari - Dept. of Radiology, Sassari, Italy; 3. University of Sassari - Institute of Hygiene, Sassari, Italy; 4. University of Sassari - Dept. of Pathology, Sassari, Italy; 5. New York University School of Medicine, NY Harbor Healthcare System VAMC, New York, NY; 6. Oncological Hospital of Cagliari - Dept. of Radio-oncology, Cagliari, Italy.*

Introduction: Magnetic resonance imaging (MRI) have been widely used in evaluation of patients with newly detected breast cancer, however its role in preoperative planning remains controversial. We investigated whether preoperative (MRI) influence surgical planning, rates of positive margins, and mastectomy rates, when added to preoperative work-up of patients with infiltrating carcinoma (IBC) eligible for breast conserving surgery (BCS). Methods: This is a retrospective analysis on 237 patients with IBC suitable for BCS on the basis of standard triple assessment (i.e. physical exam, mammography and ultrasonosgraphy) and treated during the period January 2009-June 2011. Of those, 109 underwent preoperative MRI (46%, MRI-group) and 128 did not (54%, no-MRI group). Variations in surgical treatment due to MRI were evaluated, and both rates of re-operations for initial positive margins and mastectomy rates compared in the two study groups. Results: Demographic data, histopathological characteristics, and tumor stage were similar. Tumor size was bigger in the MRI-group (16.8 mm vs. 13.9 mm, $p<0.001$). MRI changed the initial surgical planning in 18/109 patients (16.5%). Reasons for change in treatment plan included detection of larger tumor diameter requiring wider resection (8 cases, 7.3%) or finding of additional malignant lesions in either ipsilateral (9 cases, 8.2%) or contralateral breast (1 case, 0.9%). MRI-triggered treatment changes were mastectomy (N=12), wider excision (N=5) and contralateral BCS (N=1). Rates of re-excision for positive margins after primary BCS attempt appeared higher in the no-MRI group (4.1% vs 8.6%) but the difference missed statistical significance ($p=0.9$). Overall mastectomy rates were higher in the MRI-group (13.7% vs 7.0%, $p<0.05$). Conclusions: In our experience preoperative MRI altered the original treatment plan in more than 16% of patients. MRI was associated with higher mastectomy rates justified by detection of additional foci of carcinoma, but did not significantly reduce the re-excision rates for positive margins.

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Evaluating One Versus Two Day Preoperative Lymphoscintigraphy Protocol for Sentinel Lymph Node Biopsy in Breast Cancer M.G. Mount,* N.R. White, C.L. Nguyen, R.K. Orr, R.B. Hird. *Surgery, Spartanburg Regional Healthcare System, Spartanburg, SC.*

Introduction: Sentinel Lymph Node Biopsy (SLNB) is routinely used to detect axillary lymph node metastases in breast cancer patients. Preoperative radiocolloid injection with lymphoscintigraphy (PL) is routinely performed in the nuclear medicine department prior to SLNB. Few comparisons between 1 and 2 day PL protocols exist. Opponents of a 2 day protocol have expressed concerns of washout of the radiotracer to non-sentinel lymph nodes. Proponents cite lack of scheduling conflicts between PL and surgery in favor of a 2 day protocol. Methods: 387 consecutive patients with clinically node negative breast cancer underwent SLNB with PL at a single institution by 2 surgical oncologists. Data were retrospectively collected regarding PL technique and results, as well as tumor pathology. Lymphoscintigraphy images were obtained within thirty minutes of radiocolloid injection. Sentinel Lymph Nodes (SLN) were defined as nodes that had gamma counts of at least 10% of the hottest SLN or evidence of blue dye staining. Axillary lymph node dissection (ALND) was performed if the SLN could not be identified. Students T-test and X2 test were used for statistical analysis. Results: 212 patients were included in the 2 day PL group and 175 patients in the 1 day PL group. Lymphoscintigraphy identified an axillary sentinel node in 143/212 (67.5%) of patients in the 2 day group and 127/175 (72.5%) in the 1 day group ($p=0.28$). SLN was identified at surgery in 209/212 (98.6%) patients in the 2 day group and 174/175 (99.4%) in the 1 day group ($p= 0.41$). Average of 3.00 SLN were found at surgery in the 2 day group compared to 3.15 in the 1 day group ($p=0.43$). SLN was positive for metastatic disease in 54/212 (25.5%) patients in the 2 day group compared to 40/175 (22.9%) in the 1 day group ($p=0.55$). Conclusions: A 2 day lymphoscintigraphy protocol allows reliable detection of the SLN, of positive SLN and equivalent SLN harvest compared to a 1 day protocol. The timing of radiocolloid injection prior to SLNB can be left at the discretion of the surgeon.

P94

The Evaluation of Patients with Nipple Discharge: How Much is Too Much? D. Manjoros,* J.J. Alberty-Oller, T.G. Frazier, A. Barrio. *Bryn Mawr Hospital, Bryn Mawr, PA.*

INTRODUCTION: Nipple discharge accounts for 7% of all breast complaints. The diagnostic evaluation of patients with nipple discharge (ND) is often extensive and potentially uneconomical. The aim of this study was to determine the diagnostic value of cytology, prolactin and ductoscopy in patients with ND. METHODS: Following IRB approval, we retrospectively identified 360 patients with an ICD-9 code of 611.79 from January 2007 to July 2012; 139 (39%) were available for review. Patients were classified as having suspicious ND if they met 2 of 3 criteria (spontaneous, single duct or bloody/serous). RESULTS: Of the139 patients presenting with ND, 126 (91%) were reproducible on exam and 13 were not. Sixty-four (51%) had suspicious ND, 40 (32%) had physiologic, and 22 (17%) could not be classified. Cytology was performed in 114 (91%) patients with ND including 58 (91%) patients with suspicious ND and 29 (73%) with physiologic ND. Cytology demonstrated malignant cells in 1 patient (<1%) whose imaging was highly suspicious for malignancy. Four patients (3.5%) had atypia on cytology and went onto duct excision. Three were benign and 1 was malignant as suggested by imaging. Prolactin was performed in 25 (19.8%), and elevated in 1 (4%) as a result of medication. Thirty-four patients had surgery, of which 7, or 5% of the entire cohort, were malignant. Ductoscopy was performed in 9/34 (26.5%) surgery patients and did not reliably predict malignancy or papillary lesion (PPV = 0% and 67%, respectively). Cost analysis reveals a total cost of $253/patient for cytology, $159/patient for prolactin and $675/patient for ductoscopy. In this patient cohort, omission of these studies could have resulted in a total cost savings of $38,892. CONCLUSION: The addition of cytology, prolactin, and ductoscopy did not change management or surgical decision making in patients presenting with nipple discharge. Physical exam and imaging alone are reliable determinants of patients at high risk for malignancy without the added costs associated with cytology, blood work and ductoscopy.

Clinical presentation and evaluation of patients with malignancy in the nipple discharge cohort

Case Number	Age	Presentation	Mass/ thickening on exam	Cytology	Imaging	Image Guided Biopsy	Surgical Pathology
26	58	Bloody, spontaneous, multiduct	Yes	Not done	Suspicious	DCIS	IDC
49	35	Bloody, spontaneous, single duct	No	Malignant	Suspicious	IDC	IDC
81	84	Bloody, spontaneous, multiduct	Yes	Papillary	Suspicious	ILC	ILC
95	68	Serous, spontaneous, single duct	No	Papillary	Negative	No biopsy[b]	DCIS
98[a]	48	Creamy, spontaneous, multiduct	No	Papillary	Suspicious (right)	DCIS	DCIS
98.1	48	Bloody, spontaneous	No	Benign	Negative (left)	No biopsy[b]	DCIS
108	66	Bloody, single duct	Yes	Atypia	Suspicious	DCIS	Invasive papillary carcinoma
122	57	Bloody, spontaneous, single duct	Yes	Benign	Negative	No biopsy[b]	DCIS

[a]Patient presented with bilateral discharge on exam.
[b]These patients had no target on imaging for biopsy and proceeded directly to duct excision.

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Early Response Detected by Shutter-speed Dynamic Contrast-enhanced Magnetic Resonance Imaging Predicts Complete Pathologic Response of Breast Cancer to Neoadjuvant Chemotherapy
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Introduction: Obtaining accurate data regarding breast cancer response to neoadjuvant chemotherapy (NAC) is necessary to guide systemic therapy and surgical treatment. By measuring functional changes in tumor vascular properties, quantitative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been shown to be effective in detecting response to NAC in breast cancer. We report our initial experience using the Shutter-Speed model (SSM) pharmacokinetic analysis of DCE-MRI data in early prediction of pathologic response to NAC in locally advanced breast cancer. Methods: Between November 2010 and July 2012, 10 patients with pathologically proven breast cancer who underwent NAC followed by surgical resection were prospectively entered into a DCE-MRI study to evaluate response to NAC. Imaging was performed after 1, 3, and 6 cycles of NAC. Measured MRI parameters included tumor size and pharmacokinetic biomarkers, such as volume transfer constant (Ktrans) and intravasation rate constant (kep), following SSM analysis. The difference in Ktrans estimation between SSM and a standard pharmacokinetic model (ΔKtrans) was also calculated. Results: Following NAC, 3 patients were pathologic complete responders (CR), 3 partial responders (PR) and 4 with stable disease (SD) based on RECIST criteria. After only 1 cycle of NAC, SSM DCE-MRI detected significant decreases in Ktrans (-66.3% vs. 19.5%, p=0.017), ΔKtrans (-89.7% vs. 80.8%, p=0.029), and kep (-77.1% vs. 50.8%, p=0.02) in CR compared with non-CR (PR + SD). There was no statistically significant difference in tumor size between CR and non-CR after 1 cycle of NAC. Conclusions: Preliminary results demonstrate that SSM DCE-MRI detects early vascular changes in breast tumors after initiation of NAC which is more sensitive than tumor size measurement at predicting complete pathologic response. While this predictive data from SSM DCE-MRI after one cycle of NAC could be useful in guiding systemic therapy and surgery, validation of these findings and impact on treatment planning is required in a larger study.

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Definitive Surgical Treatment for Women with DCIS in a Rural Setting
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Introduction: Following the introduction of breast conservation surgery (BCS) as a treatment choice for breast cancer, its use continuously increased until 2002 when mastectomy began to make a resurgence in the surgical treatment of breast cancer. The purpose of this study was to determine if the use of mastectomy in the Appalachian region reflects this national trend and to identify factors associated with patients' treatment decisions. Method: A retrospective review of 304 patients in the Appalachian region with the diagnosis of DCIS between 2004 and 2011 was performed. Multiple variables were analyzed including: age, race, presence of comedonecrosis, tumor size, histologic grade, multifocal disease, and distance from the treatment center. Results: The mastectomy rate from 2004-2007 (Group 1, G1) was 39.25%, and from 2008-2011 (Group 2, G2) it increased to 53.52% ($p<0.05$). A statistically significant increase in the contralateral prophylactic mastectomy rate (G1 39.6% vs. G2 58.2%, $p<0.05$) and the use of Breast MRI (G1 4% vs. G2 16%, $p<0.05$) were also observed, but the use of breast reconstruction did not increase. Larger tumor size (BCS 1.309±1.10cm vs. 2.199±1.74cm, $p<0.05$) and the presence of multifocal disease (BCS 12% vs. M 61%, $p<0.05$) both correlated with the choice for mastectomy. Age, race, sex, histologic grade, presence of comedonecrosis, and distance from treatment center were not found to significantly correlate with either treatment choice. There was a trend toward mastectomy patients living further away (BCS 17.84±21.70 miles vs. M 25.16±35.40 miles, p=0.059). Conclusions: Patients in the Appalachian region appear to be choosing mastectomy for the treatment of DCIS with an increasing frequency, even greater than the national trend. The rates of both prophylactic contralateral mastectomy and breast MRI also increased during this time period. Tumor size and multifocality were the only variables associated with the choice to have a mastectomy. There was a trend for distance from treatment center being a relevant factor as shown in previous studies.

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Breast Specific Gamma Imaging Impacts Treatment Planning for Newly Diagnosed Breast Cancer
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INTRODUCTION: Numerous decision pathways exist for treatment of newly diagnosed breast cancer. A thorough evaluation of all breast tissue is essential when considering breast conservation or partial breast irradiation. We evaluated the impact of BSGI in management of newly diagnosed breast cancer. METHOD: Analysis of prospectively gathered data on BSGI studies performed in a Community Breast Health Center. IRB guidelines were observed. RESULTS: There were 1480 BSGI studies reviewed 539 were performed for a new diagnosis of cancer. Four hundred sixty one (461) studies were positive of those 81 were positive outside of the known cancer site. Additional cancer was found on pathology in 50 patients (22 ipsilateral, 16 contralateral, 11 other area including nodal metastasis and 1 bilateral) and 31 were benign (specificity 92%). A Positive BSGI demonstrates a high probability of the presence of additional disease. Treatment options were changed from breast conservation to mastectomy or neo adjuvant therapy. CONCLUSION: BSGI detected additional cancer sites in 9.3% of the newly diagnosed population. It effectively identified synchronous cancers, which impacted management. BSGI is an excellent imaging study alternative in this clinical setting.

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Presentation and Treatment Decisions among Minority Breast Cancer Patients
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Background: Located in the South Bronx, Lincoln Medical and Mental Health Center serves a diverse population, composed almost exclusively of racial minorities. The socioeconomic status of the local population is also ranked among the lowest in the nation. The institution maintains an aggressive breast cancer screening, treatment and surveillance program, which provides a full spectrum of screening, diagnostic, treatment and reconstruction options for the community. This study evaluates the effect of this community involvement on presentation of breast cancer and patient treatment decisions. Methods: A single institution prospective database was reviewed for all breast cancers diagnosed from 1/1/2006 to 12/31/10. Continuous data are presented as mean +/- SD. Results: 239 patients were identified; 1 male, 238 females. Mean age was 57.3 +/- 13.1 yrs, (range 25 – 94). The majority of patients (n=169, 69.8%) identified themselves as being of Hispanic descent; among those self-identified as Hispanic, Dominican (30.2%) and Puerto Rican (27.8%) were the most common origin. Among non-Hispanics, 80.1% were African American, 6.8% white, 6.8% Indian/Pakistani, 4.1% Filipino. Stage distribution as follows: O: 11.4%, I: 38.3%, II:26.4%, III:16.0 IV: 7.8%. Among Hispanic patients, 78% presented with localized disease. Amongst invasive tumors, 92.7% were ductal, 5.2% lobular and 2.1% mixed. Mean size of invasive tumors was 2.2 +/- 2.0 cm. 49.5% underwent partial mastectomy and 31.7% mastectomy. Among patients undergoing mastectomy, 64.4% chose to have no reconstruction, 22.0% chose implant reconstruction and 13.6% autologous flap reconstruction. Conclusion: It has been observed that women with breast cancer in minority populations present with later stage disease; this has been particularly noted among Hispanic women. This study indicates that with an aggressive community screening program, earlier stages of presentation can be achieved. Although a high rate of breast conservation is observed, the majority of patients undergoing mastectomy choose to not undergo reconstruction, and those that do, most commonly choose implant reconstruction.

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Non-invasive Nodal Staging in Breast Cancer Patients Using Gadofosveset-enhanced Magnetic Resonance Imaging
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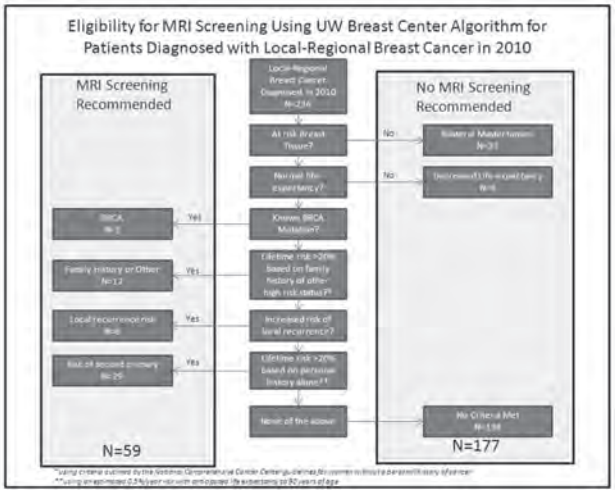
Objectives To evaluate whether axillary lymph nodes show enhancement on MRI after gadofosveset administration, to assess the time to peak enhance-

ment and to determine the diagnostic performance of gadofosveset-enhanced MRI for axillary staging. Material and Methods Ten women diagnosed with invasive breast cancer (> 2 cm) underwent both non-enhanced and gadofosveset-enhanced 3D T1 weighted axillary MRI. Signal intensity (SI) of axillary lymph nodes and different adjacent tissues was measured and relative SI (rSI) calculated. A Wilcoxon-signed-rank test was used to compare results of rSI between different time-intervals. A radiologist evaluated all lymph nodes. All MRI depicted lymph nodes were matched with lymph nodes removed during surgery. Nodal status was investigated by a pathologist. Sensitivity, specificity, PPV, and NPV values of gadofosveset-enhanced MRI for axillary lymph node staging were calculated. Results After contrast administration, significant signal increase was observed in lymph nodes ($p \leq 0.05$). When compared to muscle or fat, rSI of lymph nodes demonstrated a significant post-contrast peak enhancement between 11m30s and 20m50s ($p<0.05$). 152 lymph nodes were harvested during sentinel lymph node biopsy or axillary lymph node dissection of which 116 were matched with lymph nodes depicted on MRI. Histopathological examination resulted in 21 macro-metastases and 8 micro-metastases. Using contrast-enhanced MRI, 20 lymph nodes were rated as true positive, 83 as true-negative, 4 as false positive, and 9 as false negative. This resulted in an overall node-by-node sensitivity, specificity, PPV and NPV of 69 %, 95 %, 83% and 90 %, respectively. If micro-metastases were excluded from analysis, MRI showed a sensitivity of 86 % and a specificity of 94 %. Calculated PPV and NPV were 75 % and 97 %, respectively. Conclusion: Axillary lymph nodes show enhancement on MRI after gadofosveset administration, with peak enhancement between 11m30s and 20m50s. Diagnostic performance of gadofosveset-enhanced axillary lymph node imaging in breast cancer patients is promising, but further studies need to confirm these results.

P100

Assessment of an Algorithm to Guide MRI Screening in Patients with a Personal Breast Cancer History B. Dull,[1] A. Tevaarwerk,[2] R. Strigel,[3] B. Anderson,[4] A. Stella,[2] H.B. Neuman.[1]* *1. Surgery, Division of Surgical Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI; 2. University of Wisconsin Carbone Cancer Center, Madison, WI; 3. University of Wisconsin School of Medicine and Public Health, Department of Radiology, Madison, WI; 4. University of Wisconsin, Department of Radiation Oncology, Madison, WI.*

Introduction: Limited data exists to recommend for or against the use of screening breast MRIs for women with a personal breast cancer history. We developed an algorithm incorporating family history, and risk of local recurrence or second primary cancer to guide consideration of screening MRI for these patients at our breast center (figure). The aim was to examine projected utilization of screening breast MRI using this algorithm and its comprehensiveness. Methods: Charts of patients <80 years of age diagnosed and treated in 2010 with stage 0-III breast cancer at the UW Breast Center (n=236) were retrospectively reviewed. Patient and tumor characteristics were abstracted. Current MRI screening, algorithm eligibility for screening, and reasons for or against MRI screening were assessed. Results: Median age was 58 years (range 28-79). AJCC stage was DCIS for 19%, stage 1 39%, stage 2 30% and stage 3 12%. 82% were ER/PR and 11% Her2neu positive. Breast conservation was performed in 64%, with 25% and 11% having unilateral and bilateral mastectomies, respectively. Eight patients (3%) were BRCA positive; 28% had a first degree relative with breast cancer. 41% had extremely or heterogeneously dense breasts. Overall, 9% currently received MRI screening (6 BRCA/family history, 4 occult primary, 8 young age/breast density, 2 other). After algorithm implementation, this is projected to increase to 25% (figure). 4/20 patients currently receiving MRI screening (most commonly for occult primary) would no longer be eligible for MRI screening. Furthermore, as the algorithm does not account for breast density, 68% (13/19) patients with extremely and 56% (44/78) patients with heterogeneously dense breasts would be ineligible. Conclusion: We developed an algorithm to guide MRI screening in patients with personal breast cancer histories with plans to prospectively implement at the UW Breast Center. Projected increased utilization is modest and does not exceed current capacity. However, prior to implementation, consideration of algorithm expansion to incorporate breast density is necessary to ensure acceptability to oncologists providing breast cancer surveillance.



P101

Patient Factors Predictive of Unilateral Mastectomy Versus Bilateral Mastectomy Including a Contralateral Prophylactic Mastectomy L. Steward,[1] T. Martin-Dunlap,[1] F. Gao,[1] C. Fisher,[2] J.A. Margenthaler.[1]* *1. Department of Surgery, Washington University School of Medicine, St. Louis, MO; 2. University of Pennsylvania, Philadelphia, PA.*

Introduction: Recent data suggest an increased rate of mastectomy with or without contralateral prophylactic mastectomy (CPM) despite potential eligibility for breast conservation. We sought to determine the patient and clinical characteristics impacting this decision-making process. Methods: A questionnaire was administered to patients who underwent unilateral mastectomy (UM) or bilateral mastectomy (BM) for breast cancer between 2006 and 2010. The survey queried on demographics, surgical choices, and rationale for those choices. A chart review determined tumor characteristics and treatment information. Data were analyzed using Fisher's Exact and Chi Square tests. A p-value <0.05 was considered significant. Results: Of 310 patients, 175 underwent UM and 135 underwent BM (mean age 56 +/- 12 years). Of 135 women undergoing BM, 16 (12%) had bilateral breast cancer, while 119 (88%) had unilateral breast cancer with a CPM. Women who were <50 years and Caucasian were more likely to choose BM over UM (p=0.0001). Tumor size, stage, grade, lymph node status, or biomarker status were not predictive (p>0.05). Of 106 women who underwent genetic testing, 34 (32%) had a BRCA or p53 mutation, while 72 (68%) had no known genetic abnormality. Patients with a genetic mutation were more likely to undergo BM compared to those without a known mutation (p=0.003). Women who underwent BM more often reported that they "felt mastectomy would improve my survival" or "felt I would live long enough to be at risk for another cancer" on the questionnaire than those who underwent UM [36 (57%) vs. 25 (37%), p=0.035 and 20 (32%) vs. 5 (7%), p=0.001, respectively]. Conclusions: Patient factors, rather than tumor characteristics, impacted the decision for BM versus UM in our study population. Women who were younger, Caucasian, and those with a known hereditary cancer syndrome were more likely to undergo BM. The most common reasons cited for choosing BM over UM were a perceived improved survival and reducing risk for recurrence and/or second primaries. Future studies will focus on the role of patient education in this decision-making process.

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Breast Cancer in the Elderly: Diagnosis and Treatment E. Gates,* A. Larkin, A. O'Connor, R. Quinlan, G. Vijayaraghavan, A. Sharron, G. Whalen, B. Ward. *Univeristy of Massachusetts Memorial Medical Center, Worcester, MA.*

Introduction:Age is an independent risk factor for the development of breast cancer and screening mammography is associated with decreased breast cancer mortality. Current guidelines regarding screening mammograms in the elderly

are not standardized, and variable co-morbidities in this group make treatment a challenge. Currently the US Preventative Services Task Force has no recommendations for or against screening patients ≥75 and other national guidelines do not specify an age cutoff for screening resulting in inconsistency in diagnosis modalities and treatment in the elderly. The purpose of this study was to analyze our institution's breast cancer detection methods, and treatment in patients 75 years and older. Methods: A retrospective review of a university based cancer registry from July 2008 to January 2012 was performed. 199 patients were diagnosed with breast cancer at age ≥75. 10 patients were excluded from the study because of non-breast primary pathology or insufficient data. Those included in the study were divided into 2 groups, those diagnosed by screening mammogram and those diagnosed clinically. All patients were analyzed to assess cancer stage and treatment received. Results: 189 patients with breast cancer were analyzed. Of these, 105(55.56%) were diagnosed by screening mammogram and the remaining 84(44.44%) were diagnosed clinically. The average age at diagnosis was 80.37 years for the screening group, 82.55 years in the clinical group. In comparing stage at diagnosis, the screening group was diagnosed at an earlier stage (19.05% stage 0, 63.81% stage 1, 14.29% stage 2, 1.9% stage 3, 0.95% stage 4) compared to the clinical group (4.76% stage 0, 20.24% stage 1, 48.81% stage 2, 13.10% stage 3, 10.71% stage 4, unknown 2.38%). 95.77% of patients received some form of treatment (100% in the screening group, 90.4% in the clinical group). Conclusion: In the 75 and older population, screening mammography was still the most common method of breast cancer detection and the patient population diagnosed by screening mammogram had earlier stage cancer at diagnosis. The majority of patients in both groups received treatment. This suggests there is a role for screening mammograms within the elderly.

Parameters	Screening	Clinical
Total Breast Cancer Diagnosis	105 (55.56%)	84 (44.44%)
Average Age at Diagnosis	80.37	82.55
Age Range	75-93	75-101
Cancer Stage		
0	20 (19.05%)	4 (4.76%)
1	67 (63.81%)	17 (20.24%)
2	15 (14.29%)	41 (48.81%)
3	2 (1.9%)	11 (13.10%)
4	1 (0.95%)	9 (10.71%)
Unknown	0 (0%)	2 (2.38%)
Treatment		
Surgery	103 (98.1%)	60 (71.43%)
Radiation	48 (63.81%)	34 (40.48%)
Endocrine Therapy	67 (45.71%)	50 (59.52%)
Chemotherapy	4 (3.81%)	12 (14.29%)
No Treatment	0 (0%)	8 (9.52%)
Total Treated	105 (100%)	76 (90.48%)

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Histopathological Characteristics Associated with Atypical Lobular Hyperplasia and Lobular Carcinoma *In Situ* Diagnosed on Image-Guided Core Biopsy and the Rate of Upgrade to Ductal Carcinoma *In Situ* or Invasive Cancer on Subsequent Excisional Biopsy

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Introduction: Atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) are proliferative lesions of the breast. When identified by percutaneous core biopsy, these lesions are routinely surgically excised based on data suggesting rates of upgrade to ductal carcinoma in situ (DCIS) or an invasive cancer from 3.1-25%. The aim of this study was to examine the ALH and LCIS core biopsy database to determine associated histopathologic markers of increased risk of upgrade. Methods: Retrospective analysis of the medical records of 215 patients diagnosed on core biopsy with ALH or LCIS was performed. Patient age, relevant history and core biopsy pathologic findings were recorded. Results: Overall, the combined upgrade rate for ALH and LCIS was 13.5% (29/215). Eighteen of 179 (10%) core biopsies containing ALH were upgraded on final surgical pathology to DCIS (11/18, 61%), invasive ductal cancer (3/18, 17%), and invasive lobular cancer (4/18, 22%). Four (5.5%) of the core biopsies with ALH associated with calcifications and 14 (13%) of the ALH biopsies without calcifications were upgraded (p=0.09). Lesions noted on pathology reports as focal ALH (60/179) had a 15% upgrade rate (9/60) to DCIS (6/9, 67%), invasive ductal cancer (1/9, 11%) or invasive lobular cancer (2/9, 22%). Eight of 9 were not associated with calcifications (p=0.42). Thirty one percent (11/36) of patients with core biopsy findings of LCIS resulted in upgrade—36% DCIS, 55% lobular and 9% tubular cancer. LCIS with and without calcifications on biopsy was upgraded to DCIS or invasive cancer in 8/24 (33%) and 3/12 (25%) respectively, (p=0.71). The presence or absence of calcifications in association with LCIS had no bearing on upgrade (33% vs. 25%). Conclusion: Our institutional experience, one of the largest studies of ALH and LCIS, shows that a significant portion of excisional biopsies are associated with a diagnosis of DCIS or invasive cancer. Neither the presence nor absence of calcifications, nor the descriptor of focal ALH delineate a group of patients who do not require re-excision.

P104

Comparison of Breast Tumors with Increased HER2 Copy Number With and Without Polysomy 17 L.A. Field,[1]* B. Deyarmin,[1] R.E. Ellsworth,[2] C.D. Shriver.[3] *1. Windber Research Institute, Windber, PA; 2. Henry M. Jackson Foundation for the Advancement of Military Medicine, Windber, PA; 3. Walter Reed National Military Medical Center, Bethesda, MD.*

Approximately 20% of invasive breast cancers overexpress HER2 and are associated with decreased relapse-free and overall survival. Her2 overexpression is primarily due to amplification of the HER2 oncogene on chromosome 17, and these patients are typically treated with targeted therapies such as trastuzumab or lapatinib. However, increased HER2 copies may also result from chromosome 17 polysomy. The clinical benefit of treating patients with polysomy 17 in the absence of HER2 amplification with targeted therapy remains unclear. Herein, we have compared the clinical characteristics and gene expression profiles of breast tumors with increased HER2 copy numbers due to HER2 amplification or chromosome 17 polysomy. HER2 and CEP17 copy numbers were determined. Only those patients with at least 4 HER2 copies per cell were included in the analysis; those with a HER2/CEP17 ratio <2.2 were considered polysomic (N=29) while those with a ratio >2.2 (N=44) were considered amplified. Tumor grade and size did not differ between polysomic and amplified samples. Although amplified cases tended to be younger at diagnosis and less likely to be diagnosed with Stage I tumors, this difference did not reach statistical significance. HER2 amplified tumors were more likely to be ER negative (P=0.027) and have lymph node metastases (P=0.028). Comparison of polysomic (N=14) and amplified (N=18) cases by gene expression microarray identified 67 genes that were differentially expressed (P<0.01; fold change >2) between the two groups. These genes are involved in cell cycle control, cell adhesion and migration, cell differentiation, cytoskeleton organization, signal transduction, protein synthesis and degradation, and ion transport. Interestingly, the top 4 most significant genes with higher expression in the polysomic samples, including TUBG1, CPD, BLMH, and JUP, are all located on 17q. Currently, it is not clear whether treatment with targeted Her2 therapy is beneficial in patients with polysomy 17. However, the genes identified here may represent novel targets for developing new treatments that are effective in these women and require further study.

P105

Factors Associated with Non-Receipt of Accelerated Partial Breast Irradiation (APBI) in Early-Stage Breast Cancer N.A. Dallas,[1]* I. Bedrosian,[1] L.R. Allen,[1] E.S. Bloom,[2] S.F. Shaitelman,[2] E.A. Mittendorf,[1] W. Woodward,[2] W. Tereffe,[2] H.M. Kuerer,[1] K. Hunt,[1] R. Alvarado,[1] G. Babiera.[1] *1. Department of Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX; 2. Department of Radiation Oncology, UT MD Anderson Cancer Center, Houston, TX.*

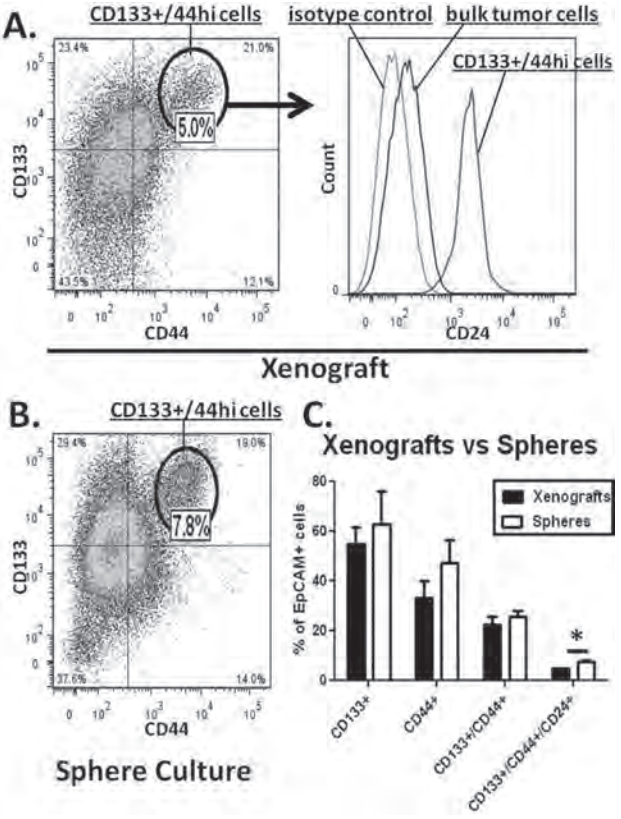
Purpose: Use of catheter-based APBI as adjuvant therapy for patients with early-stage breast cancer is increasing. Little is known about rates of receipt of APBI in women deemed eligible. This study sought to identify factors associated with non-receipt of APBI among APBI candidates during initial experience of an APBI program. Methods: Review of a prospective database identified 435 invasive breast cancer patients between 2009-2011 who fulfilled screening criteria for APBI: age>50, preop unifocal tumor size

< 3cm, clinically node negative axilla, and breast conserving therapy. Final criteria to confirm eligibility were: pathologic tumor <3cm, >2mm margin, no LVSI, and pN0 status. Neoadjuvant therapy patients were excluded. Clinicopathologic data and details of adjuvant therapy were recorded. Fisher's and Wilcoxon rank sum tests were used to identify factors related to non-receipt of APBI. Results: Of 435 patients who met preop APBI criteria, 33 refused any radiation and were excluded from the analysis. Among 402 evaluable patients, 6 (1%) had wound complications and 117 (29%) had final pathologic findings rendering them ineligible for APBI. Of the remaining 279 who were eligible, 62 (22%) had attempted catheter placement. One patient did not complete APBI therapy due to radiation planning constraints. Univariate analysis of clinicopathologic factors failed to identify any that would predict who would remain an APBI candidate after surgery. Among the 221 patients eligible for APBI who did not receive it, the only predictors of non-receipt were surgeon and radiation oncologist involved in the patient's care (p<.0001). Over time, there was an increase in recommendation of APBI therapy for APBI candidates (R2=.87). Conclusion: Our findings reflect current national trends of increasing APBI use among clinicians. Approximately one-third of patients with invasive disease who are deemed APBI candidates preoperatively fall out of subsequent consideration for APBI, mostly due to factors noted on final pathology. Non-conformance of the catheter to the cavity and surgical complications were minor contributors to non-receipt of APBI.

P106

Colorectal Liver Metastases Demonstrate Sub-populations with Differing Cancer Stem Cell Phenotypes in Xenograft and *In Vitro* Models D.E. Sanford,* A. Giorgi, B.D. Goetz, R.Z. Panni, W.G. Hawkins, D.C. Linehan, P. Goedegebuure, R.C. Fields. *Washington University in St. Louis, St. Louis, MO.*

Background: Tumors are composed of heterogeneous cell populations, some of which demonstrate enhanced tumor-forming capabilities (so-called tumor initiating cells [TIC] or cancer stem cells). In colorectal cancer (CRC), CD133, 44, and 24 are cell surface markers that identify TIC. Therefore, we sought to determine if CRC liver metastases (CRC-LM) form xenografts (in vivo) and cell cultures (in vitro) with TIC markers. Methods: CRC-LM were grafted in NOD/SCID mice and passaged serially. Xenografts were mechanically dissociated and cultured under sphere forming conditions. Flow cytometry was performed for TIC phenotype. Results: 16 of 18 (89%) CRC-LM specimens formed tumors in NOD/SCID mice. Xenografts formed EpCAM+ tumors and spheres (>90% EpCAM+ cells). The frequency of CD133+, CD44+, and CD133+/CD44+ tumor cells were 55%±7%, 33±7%, and 23%±3%, respectively. There was a subpopulation within the CD133+/CD44+ cells that expressed elevated levels of CD44 (CD44hi). This CD133+/CD44hi population was also CD24+; representing 5%±0.1% of all xenograft cells (Fig.A). Eight of eleven (73%) xenografts formed spheres in vitro. The frequency of CD133+, CD44+, and CD133+/CD44+ cells were 63%±13%, 47%±9%, and 26%±2%, respectively. CD133+/CD44+/CD24+ cells made up 8%±0.6% of all sphere-forming cells (Fig. B). There was a non-significant trend towards increased frequency of CD133+,CD44+, and CD133/CD44 positive cells in the spheres compared to the xenografts (Fig.C). However, the percentage of CD133+/CD44+/CD24+ triple-positive cells was significantly increased in the spheres relative to the original xenografts (7.6%±0.6% in spheres v. 4.8%±0.1% in xenografts, respectively; p<0.05; Fig. C). Conclusion: CRC-LM derived xenografts and spheres are composed of distinct cell populations with differing levels of TIC/cancer stem cells. Sphere cultures may enhance for the most enriched TIC population (CD133+/CD44+/CD24+ triple-positive). Thus, xenografts and sphere cultures are important model systems for further characterization of the importance of cancer stem cells in CRC progression and metastases.

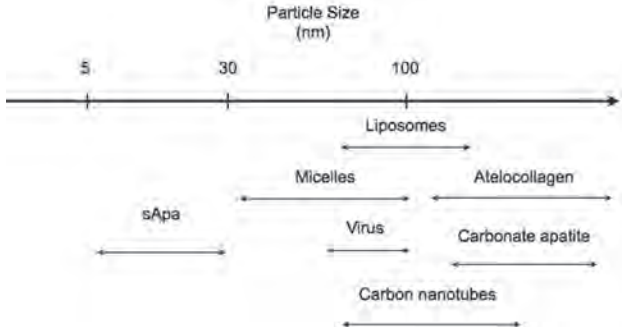


P107

Superb Effects on Systemic siRNA Delivery by pH-sensitive Super Apatite Ultra-Nanoparticles X. Wu,* H. Yamamoto, M. Uemura, N. Haraguchi, T. Hata, J. Nishimura, I. Takemasa, T. Mizushima, Y. Doki, M. Mori. *Department of Surgery, Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan.*

Background: Particle size becomes a crucial factor that should be taken into account when engineering an in vivo systemic carrier. Recent nanoparticle siRNA delivery systems often result in distribution to normal organs, possibly due to the relatively large size of the nanoparticles (approximately 100 nm). At present, the tissue distribution and tumor accumulation of nanoparticles ranging from 5 to 30 nm remain to be uncovered. Here, we introduce a super apatite (sApa) delivery system that is expected to surmount the limitations of the current carriers by employing 10-nm ultra-nanoparticles. sApa ultra-nanoparticels consisting of inorganic ions are highly stable at the physiological pH 7.4, and quickly degradable at pH 5.5 in the endosomal compartments. Methods: In order to investigate the in vitro transfection efficiency of siRNA in colon cancer cells using sApa, we performed intracellular siRNA measurement assay, western blot analysis, and cell proliferation assay, compared with Lipofectamine. Furthermore, we prepared colon cancer solid tumor model to perform in vivo biodistribution study and antitumor activity study of sApa. Results: We confirmed significantly higher in vitro transfection efficiency of siRNA by sApa, comparing with Lipofectamine. Western blot analysis showed the survivin protein level decreased more rapidly when transfected by sApa than by Lipofectamine. The rapid and strong down-regulation of survivin protein expression by sApa treatment could drastically reduce (by 50%) the cell viability. As for in vivo delivery efficiency, the sApa exhibited significantly lower siRNA accumulation in liver and kidney, but higher siRNA distribution to tumors (2.7±0.26-fold) when compared with naked-siRNA–treated tumors (0.95±0.084-fold, p<0.01). Accordingly we injected i.v. sApa incorporating anti-survivin siRNA, and the tumor volume was significantly smaller

in mice treated with sApa-survivin-siRNA than that treated with sApa incorporating control siRNA or saline (p<0.001). Conclusion: The sApa delivery system is of vital use to experimental approaches both in vitro and in vivo, and ultra-nanoparticles may constitute a new avenue in nanoparticle-based medicine.



Current nanoparticle delivery systems classified in terms of size

P108

The Sphingosine-1-phosphate Receptor Modulator, FTY720, Synergizes with 5-FU and Irinotecan in Colon Cancer Cell Killing T. Aoyagi,[1]* A. Yamada,[1] M. Nagahashi,[1] S. Milstein,[2] S. Spiegel,[2] K. Takabe.[1] *1. Surgery, Virginia Commonwealth University, Richmond, VA; 2. Virginia Commonwealth University, Richmond, VA.*

Introduction:The five-year survival rate of advanced colon cancer remains low. Sphingosine-1-phosphate (S1P), a bioactive lipid mediator, plays critical roles in cancer progression. FTY720 is a functional antagonist of S1P receptor 1 and is approved by FDA for multiple sclerosis. The effects of FTY720 on colon cancer have not yet been examined. The aim of this work was to determine whether FTY720 suppresses survival of colon cancer cell lines either alone or in combination with 5-fluorouracil (5-FU) or irinotecan, the most commonly used chemotherapies for colon cancer. Methods:The effects of FTY720 on cell survival of multiple cancer types were assessed with the NCI-60 panel. Colon cancer cell-lines, human well-differentiated (DLD-1), human moderately differentiated (HT29), human poorly differentiated (HCT-116) and murine poorly differentiated (CT26) were seeded at a density of 2000 cells per well in 96-well culture plates and FTY720 and 5-FU or irrinotecan or both were added after 24 hours. Effects on cell viability were examined by WST-8 assay 48 hours later. Results:Among the 9 types of cancer cells tested in the NCI-60 panel, colon cancer and leukemia were the only ones in which all cell lines responded to FTY720. The half maximal (50%) inhibitory concentration (IC50) of FTY720 were at a concentration of less than 1.8uM in 4 colon cancer cell lines. The IC50 values for 5-FU and irinotecan were less than 8.0uM and 5.8uM, respectively, in the same 4 colon cancer cell lines. The combined treatment with FTY720 and 5FU synergistically suppressed survival. Also the combination treatment of FTY720 and irinotecan synergistically suppressed survival, except in HT29 cells. Most of the combination indices of FTY720 plus 5-FU or irinotecan on 4 colon cell lines were <1, indicating synergy. Conclusion:Our results demonstrate that FTY720 has a synergistic cell killing effect with 5-FU and irinotecan on most colon cancer cell-lines. Further studies will focus on delineating the mechanisms determining susceptibility to these drugs, and examining the effects of combining FTY720 with other commonly used chemotherapeutic drugs, such as Oxaliplatin.

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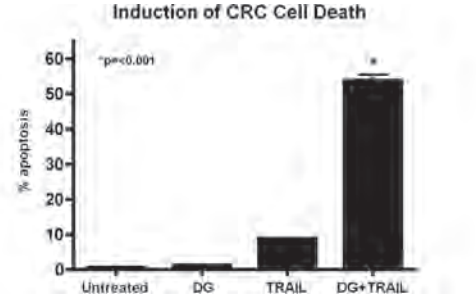
Loss of Heterozygosity (LOH) in Appendiceal Carcinomatosis (AC): Utility in Discriminating among Intermediate-Risk Patients P. Wagner,* N. Kulkarni, C. Huynh, D. Caba Molina, A.H. Zureikat, M.P. Holtzman, S.A. Ahrendt, J.F. Pingpank, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: AC can be stratified into low, medium and high risk categories on the basis of histologic grade, lymph node status, and completeness of cytoreduction. The intermediate category raises difficult treatment decisions when selecting patients for aggressive cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC). LOH and other molecular classification methods have the potential to improve selection of patients for CRS-HIPEC. Methods: LOH was assessed using microsatellite markers within 9 tumor suppressor loci known to be mutated in appendiceal or colorectal cancer: 1p36 (CMM), 3p26 (VHL), 5q23 (APC), 7q31 (MET), 9p21 (CDKN2A), 9q24 (PTCH), 10q23 (PTEN), 17p13 (TP53), and 18q21 (DCC). Patients were stratified based on the presence and degree of LOH, as quantitated by the fractional mutation rate (FMR, number of affected loci expressed as a percentage of all informative loci). LOH was tested for correlation with clinicopathologic features and oncologic outcomes in 130 patients undergoing attempted CRS-HIPEC for AC. Results: LOH was detected in 88 tumors (66%). The most frequently involved loci were 17p13/TP53 (n=26), 10q23/PTEN (n=22), and 7q31/MET (n=19). LOH at 17p13/TP53 and 10q23/PTEN were frequent as isolated abnormalities (7 cases each), suggesting that they may represent early steps in appendiceal carcinogenesis. An FMR of >25% was associated with high grade histology (55% vs. 34%, p=0.04). Progression-free survival was shorter in patients with LOH (p=0.04), a difference that was significant only among intermediate-risk, but not low- or high- risk, subgroups. A trend towards decreased overall survival (p=0.09) was associated with LOH. Individual loci were associated with 12-month survival rates ranging from 59% (18q21/DCC) to >80% (9p21/CDK2NA, 17p13/TP53). Conclusions: LOH in AC is associated with high grade histology and inferior oncologic outcomes. LOH may be helpful in identifying intermediate-risk patients who are likely to have favorable outcomes following CRS-HIPEC. Ongoing research will aim to define the pathogenic and prognostic significance of individual tumor suppressor loci in AC.

P110

Induction of Potent Tumor-specific Cell Death in Human Colorectal Cancer via the Apoptotic Pathway A.V. Maker,[1]* R. Carr,[2] J. Qin,[1] B. Prabhakar.[2] *1. Department of Surgery, Division of Surgical Oncology, University of Illlinois at Chicago, Chicago, IL; 2. University of Illinois at Chicago - Department of Microbiology and Immunology, Chicago, IL.*

Introduction TNF-related apoptosis-inducing ligand (TRAIL) can induce apoptosis in cancer cells with little or no effect on normal tissue; however, many colorectal cancers (CRC) are highly TRAIL resistant. Glucose analogues are preferentially taken up by CRC cells, a property utilized in PET scanning, and may upregulate death receptor expression on the cell surface. Therefore, the effect of glucose analog administration on TRAIL induced apoptosis in CRC cells was examined. **Methods** TRAIL resistant CRC cells were treated in vitro with a combination of deoxyglucose (DG) and TRAIL. AnnexinV/PI expression was analyzed for the effect on apoptosis and cell necrosis. Cell surface expression of the TRAIL receptors, death receptor 1 (DR1) and DR2, were assessed utilizing flow cytometry; and protein and transcript expression were determined with Western blot analysis and RT-PCR. Caspase degradation and inhibition were evaluated with Western blot analysis. **Results** TRAIL±DG had no effect on non-tumor cells. When pretreated with the glucose analog, TRAIL-resistant CRC cells were highly susceptible to TRAIL induced apoptosis and necrotic cell death compared to TRAIL alone (54± 1.6% vs. 9±0.2%, p<0.001). Caspace 3 levels and caspace 3 and 8 cleavage products on Western blot confirmed that cell death was via the apoptosis cascade initiated at the death receptor. Pan-caspace inhibition significantly inhibited the synergy induced cell death (64± 0.4% vs. 12±0.4%, p<0.0001), confirming the apoptotic mechanism. Glucose analog pretreatment significantly increased TRAIL receptor surface expression (36± 3% vs. 9±0.2%, p=0.02) and protein transcript expression (p=0.02), identifying the mechanism of action for the efficacy of this drug combination. **Conclusions** Administration of a safely tolerated glucose analog upregulated death receptor surface expression and synergized with TRAIL to induce potent tumor-specific apoptosis in even TRAIL-resistant human colorectal cancer cells. Mechanisms to sensitize resistant CRC cells to TRAIL-induced apoptosis is a promising anti-cancer strategy.



P111

Surgical Practice Patterns and Long-term Survival for Early Stage Rectal Cancer K. Stitzenberg,[1]* D. Penn,[1] H. Sanoff,[2] M.O. Meyers.[1]
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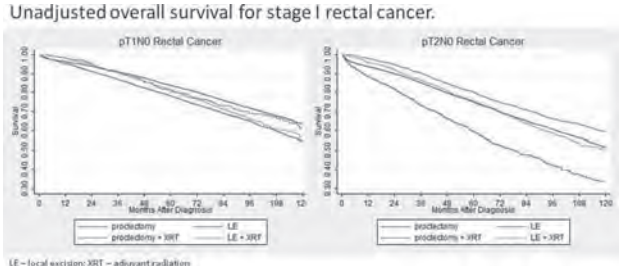
BACKGROUND: Local excision (LE) is considered a standard option only for patients with T1N0 rectal cancer and those who are medically unfit for proctectomy. The growing numbers of case series suggest that use of LE may be increasing. The objectives of this study are to characterize practice patterns for surgical management of rectal cancer and determine the comparative effectiveness of LE versus proctectomy for overall survival (OS) for Stage I rectal cancer. METHODS: National Cancer Database data were used to identify all patients with rectal cancer diagnosed from 1998-2010. Patient and tumor characteristics associated with procedure type were examined. Kaplan-Meier plots and Cox proportional hazards models, controlling for patient and tumor characteristics and receipt of radiation (XRT), were used to compare OS for Stage I cases from 1998-2005. RESULTS: 147,553 (50%) of 296,068 cases were excluded due to prior malignancy, non-invasive disease, distant metastases, failure to receive definitive surgery, treatment indicated to be palliative, or receipt of neoadjuvant therapy. 76,756 (69%) cases were treated with proctectomy and 34,697 (31%) with LE. Use of LE increased over time (1998-23%; 2010-41%, p<0.001). LE was most commonly used for Stage I cases. Women, older patients, patients with less comorbidities, black patients, uninsured patients, and those with T1 tumors were more likely to receive LE than other Stage I patients. Socioeconomic status and rurality were not associated with use of LE. Adjuvant XRT was used for 12% of T1 tumors and 46% of T2 tumors after LE and 5% of T1 tumors and 12% of T2 tumors after proctectomy. For patients with T1N0 tumors, adjusted OS was associated with receipt of proctectomy (HR 0.83; 95%CI 0.77, 0.89) but not XRT. For patients with T2N0 tumors, adjusted OS was associated with both proctectomy and XRT: LE only HR 1.0; proctectomy only HR 0.70; LE+XRT HR 0.70; proctectomy+XRT HR 0.70. DISCUSSION: Use of LE for rectal cancer is increasing. LE alone is associated with poorer long-term OS than proctectomy. For patients with larger tumors, those that receive adjuvant XRT in addition to LE have significantly better OS than those who receive LE alone.



P112

Usefulness of the Addition of Lymph Node Ratio to the 2010 Staging System for Rectal Cancer Treated with Preoperative Chemoradiotherapy P. Luna-Perez,* M. Ramírez, N. Salazar, A. Cravioto, S. Rodriguez, M. Gutierrez. *Surgical Oncology, Hospital de Oncologia. Centro Medico Nacional SXXI, Mexico City, Mexico.*

Background. Approximately 10–40% of rectal cancer patients undergoing long-course of neoadjuvant chemoradiation (CRT) had lymph node metastasis. There is little information about the usefulness of the current staging in those patients. Objective. Analyze the current staging utility in predicting recurrence and survival in patients with stage III rectal cancer after CRT. Methods. Between 1996 and 2005, 840 patients with rectal adenocarcinoma were treated with CRT (5-FU + 50.4 Gy) + surgery. 111 of them were classified as stage III. Staging was done with 7th edition of the AJCC. Factors associated with recurrence were analyzed by Cox regression analysis, survival with the Kaplan-Meier method and comparison with log-rank test. Results. There were 62 males and 49 females (7.8%), mean age was 56.2 years. Surgeries performed were: low anterior resection (50), abdominoperineal resection (41) and pelvic exenteration (20). Mean of harvested lymph nodes and metastatic lymph nodes was 19.5 and 8.8, respectively. Post-radiated surgical stages were: IIIA (15), IIIB (55) and IIIC (41). At median follow-up of 46 months, 46 (41.4%) patients developed recurrences as follows: locoregional (n = 17), local + distant (n = 2) and systemic (n = 25). Recurrences according to tumor stage were: IIIA, 0%, IIIB, 34% and IIIC, 46% (p= 0.03). Using lymph node ratio (LNR) of 0.4, 5-year disease-free survival (DFS) in those with <0.4 was 59%, conversely, 39% in those with >0.4 (p= 0.03). 5-year DFS according to stage were IIIA, 100%; IIIB, 59% and IIIC 50%, respectively (p= 0.05). 5-year DFS of those with stage IIIB and LNR <0.4 was 57%, conversely 41% in those >0.4; in IIIC with LNR <0.4 was 50%, conversely 23% in those with >0.4 (p=0.03). Associated factors with recurrence were: LNR >0.4, stage IIIC, CEA >13 ng, < 10 harvested lymph nodes and pelvic exenteration. Conclusions. The addition of LNR to the 2010 staging system for rectal cancer treated with preoperative chemo-radiotherapy is a powerful tool to identify patients with high risk of recurrence and poor survival

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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis in the Elderly P. Tabrizian,* G. Jibara, B. Shrager, B. Franssen, M. Yang, U. Sarpel, S. Hiotis, D. Labow. *Surgical oncology, Mount Sinai Medical Center, NY, New york, NY.*

Introduction Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) has gained acceptance in the treatment of peritoneal carcinomatosis with reported morbidity and mortality rates of 27%-56% and 0%-11% respectively. The safety and outcome of such major operation in the elderly remains unclear. We report our experience at a high volume tertiary center. Method: A total of 176 consecutive patients underwent CRS/HIPEC for peritoneal carcinomatosis between 07/2007 and 05/2012. Mitomycin C was administered intraperitoneally at 41C for 90 mins. Patients were categorized into two groups according to the age at the time of surgery: Group 1 (< 65 years-old) and Group 2 (≥ 65 years-old). Clinical and perioperative data of both groups were analyzed and factors associated with major morbidity (Clavien Class III-IV) were examined. Results: Of the 176 patients, 33 were 65 years or older. Characteristics of both groups are summarized in table 1. Gender, type of malignancy, estimated blood loss (> 400 ml), intraoperative blood transfusion, operative time (> 6 hours), number of bowel anastomoses, intraoperative PCI ≥ 16, and extent of cytoreduction (Δ PCI) were not associated with major morbidity in the elderly population (p> 0.05). At a median follow-up of 12.4 months(± 1.02), the median survival of the most common malignancies (colorectal and appendiceal carcinomatosis) were 31.4 (±6.3) (Group 1) and 22.5 (±3.3) (Group 2) respectively (p=NS). Conclusion: CRS/HIPEC procedures for peritoneal carcinomatosis in the elderly demonstrate acceptable perioperative outcomes in well selected patients. Optimal cytoreduction was achieved in 77.8% of cases and survival was not significantly different from that of the younger group.

Table 1: Characteristics of Group 1 (< 65 years) vs. Group 2 (≥ 65 years)

Variable	Group 1 N=143 (81.3%)	Group 2 N=33 (18.7%)	P-Value
Male Gender (%)	62 (43.4)	17 (51.5)	NS
Primary tumor site (%)			
Colorectal	42 (29.4)	10 (30.3)	
Appendiceal	46 (32.2)	10 (30.3)	
Pseudomyxoma peritonei	12 (8.4)	2 (6.1)	NS
Gastric	10 (7.0)	2 (6.1)	
Ovarian	9 (6.3)	2 (6.1)	
Others	24 (16.8)	7 (21.2)	
Operative time (minutes, mean) (±SD)	380 (±134)	342 (±91)	NS
Estimated blood loss (ml, mean) (±SD)	689.2 (±812)	986.3 (±1635.8)	NS
Blood transfusion, n(%)	51 (37.2)	15 (50.0)	NS
Intra-operative PCI score ≥16 n (%)	75 (54.0)	13 (40.6)	NS
Δ PCI, mean (±SD)	12.4 (7.2)	12.2 (6.3)	NS
CC score 0-1 n (%)	85 (72.0)	21 (77.8)	NS
Number of organs resected, mean	3.9 (±2.6)	3.6 (±1.6)	NS
Number of bowel anastomoses ≥2 n (%)	19 (15.2)	4 (14.3)	NS
Hospital stay [days], mean (± SD)	11.5 (±15.1)	12.6 (±15.8)	NS
ICU admission , n (%)	26 (18.3)	10 (30.3)	NS
Major morbidity n (%) 90 days	38 (28.4)	8 (27.6)	NS
Mortality n(%) 30 days	2 (1.4)	3 (9.1)	0.046

P114

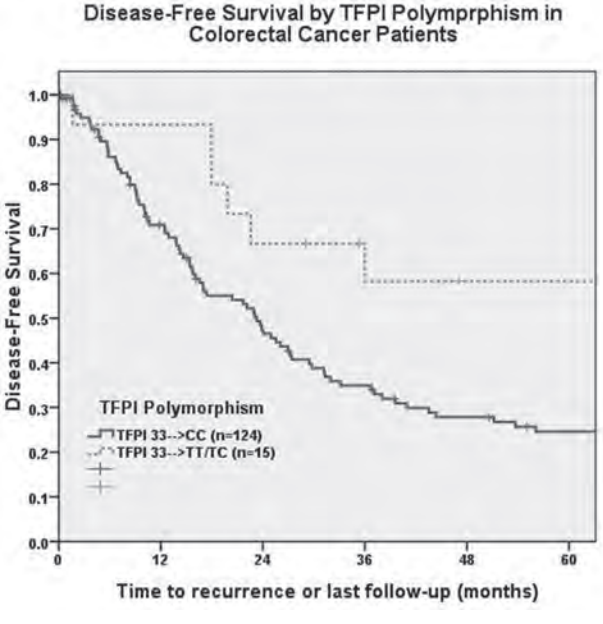
Identification of Genes that Predict Lymph Node Metastasis in Colorectal Cancer Cases Y. Takano,* R. Uchi, H. Ueo, T. Matsumura, K. Sugimachi, K. Mimori. *Kyushu University Beppu hospital, Beppu-city, oita, Japan.*

Introduction Currently, Endoscopic mucosal resection (EMR) and laparoscopic surgery with colorectal cancer (CRC) and has been expanding rapidly. In handling of colon cancer, adaptation of EMR is determined by the depth of tumor invasion. It is important to identify genes to predict lymph node metastasis in early CRC tumors precisely in a reproducible fashion to determine the adaptation of EMR treatment. We performed the comprehensive analysis of gene expression and genomic copy number simultaneously in CRC primary tumors to identify the bona-fide indicator of lymph node metastasis. Materials and methods We collected cancer cells specifically by Laser Microdissection (LMD) on 157 cases of primary colorectal cancer, and performed oligo microarrays for gene expression (GE) and aCGH for copy number aberration. As for candidate genes to be associated with lymph node metastasis, we examined reprodicibility by quantitative RT-PCR using cDNA created from the RNA extracted from 172 cases of CRC. Results As for the association of lymph node metastasis, we found that 240 genes and 54 genes by aCGH and by oligo GE microarray, respectively. According to database of those two arrays, 501 genes were significantly correlated (correlation coefficient > 0.7) with each other, and we found that 11 out of 501 genes were identified as lymph node metastasis related genes with copy number alteration. Of these 11 genes, we focused on PCM1, MTUS1, ASAH1 on 8p22. Then, we confirmed that the decreased expression and genomic deletion of MTUS1 were observed in lymph node positive cases (p=0.0092) in another subset of 172 cases of CRC. Conclusions To measure the expression of MTUS1 of the tumor by PCR, we can predict the presence of lymph node metastasis. We expected that the loss of MTUS1 should be an important marker in determining the adaptation of endoscopic resection.

P115

Tissue Factor Pathway Inhibitor Gene Polymorphism -33T—>C Predicts Improved Disease-Free Survival in Colorectal Cancer A.K. Bazzarelli,[1]* A.S. Scheer,[1] L. Tai,[2] R. Seth,[1] C. Tanese de Souza,[2] D.J. Jonker,[1] J.A. Maroun,[1] M. Carrier,[1] R.C. Auer.[1] *1. University of Ottawa, Ottawa, ON, Canada; 2. Ottawa Hospital Research Institute, Ottawa, ON, Canada.*

Introduction: Tissue Factor Pathway Inhibitor (TFPI) is an anticoagulant protein exhibiting antimetastatic properties in preclinical models. The homozygous CC polymorphism on intron 7 of TFPI (-33T—>C) is associated with higher TFPI protein levels and a lower risk of venous thromboembolism (VTE). The present study is the first to evaluate the impact of the inherited TFPI polymorphism on disease-free survival (DFS) in cancer patients following curative resection. Methods: A prospectively maintained colorectal tumour bank with associated clinical data was used to identify patients who underwent curative surgery for colorectal cancer between 1994 and 2006. Germline DNA was extracted from formalin fixed, paraffin embedded normal colonic mucosa. Single nucleotide polymorphisms (SNPs) for Tissue Factor Pathway Inhibitor (TFPI, -33T—>C), Factor V Leiden (FVL, G1691A), and Prothrombin (PT, G20210A) were determined by polymerase chain reaction. DFS was described using the Kaplan-Meier method. Multivariable regression analysis, with known prognostic factors, was performed using the Cox Proportional Hazard model. Results: Of the 139 patients identified, the prevalence of the wildtype (TT) TFPI genotype was found in 57.3% of samples, the heterozygous genotype (CT) in 29.4%, and the homozygous genotype (CC) in 10.5%. The incidence of VTE was 21.6% in the TT/TC genotypes and 6.7% in the CC genotype (p=0.4). The CC genotype was associated with superior DFS (HR=0.38, [95%CI 0.17-0.88]; p=.02) with 5 year DFS 56.3% vs. 24.6% for CC vs. TT/TC respectively. In multivariate analysis female sex (HR=0.61, p=.02), chemotherapy (HR=0.66, p=.05), node negative (HR=0.47, p=.005) and TFPI CC polymorphism (HR=0.35, p=.01) were independently associated with improved DFS. The prevalence of FVL (0.7%) and PT (2.2%) polymorphisms was too low to detect any interaction with TFPI polymorphism and DFS. Conclusions: These findings indicate that the inherited anticoagulant homozygous -33T—>C TFPI polymorphism may protect against colon cancer recurrence, and suggest a causal role for the coagulation system in cancer outcomes.



P116

KRAS Status is a Prognostic Variable in Cytoreductive Surgery/Hyperthermic Intraperitoneal Chemotherapy for Colorectal Cancer Carcinomatosis D. Magge,[1]* B.A. Boone,[1] W.E. Gooding,[2] R. Pai,[1] L. Ramalingam,[1] J.F. Pingpank,[1] M.P. Holtzman,[1] H.A. Choudry,[1] H.J. Zeh,[1] D.L. Bartlett,[1] A.H. Zureikat.[1] *1. University of Pittsburgh Medical Center, Pittsburgh, PA; 2. UPCI Biostatistics Facility, Pittsburgh, PA.*

Introduction: In patients (pts) with isolated peritoneal carcinomatosis from colorectal cancer (CRC), Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) may be an option. CRC pts who are KRAS mutants have worse prognosis, but it is unknown whether KRAS+ pts with CRC peritoneal carcinomatosis have worse overall survival (OS) compared to wildtype (WT) counterparts. We sought to determine if KRAS can be used as a prognostic variable for pts undergoing CRS with HIPEC. Methods: Of 193 pts with metastatic CRC undergoing CRS/HIPEC between 2006 and 2011, we retrospectively analyzed 70 pts with known KRAS mutation status. Kaplan Meier survival curves, log rank tests, and proportional hazards regression were used to identify factors associated with overall survival. Results: CRS/HIPEC was performed for CRC peritoneal carcinomatosis in 193 pts, and 70 pts had KRAS mutational analysis performed via DNA sequencing of codons

12/13. For the 70 pts, median peritoneal carcinomatosis index (PCI) was 9 (IQR 6-11), and complete CRS (Cytoreductive score (CC)-0/1) was achieved in 54 pts (83%). Most pts received preoperative chemotherapy (93%). Thirty four ((49%) (CI=39%-60%)) pts were KRAS positive, the remainder of whom were KRAS WT. Major postoperative morbidity (Clavien IIB/III/IV) occurred in 16 pts (23%), with no 60 day mortalities. Twenty six pts were alive with median follow-up of 18 mos (range = .3 – 53mos). Cohort median OS was 21mos (95% CI=15–33mos). The probabilities of 1 and 5 yr survival were .79 (95% CI=.70 -.90) and .06 (95% CI=.01 -.37), respectively. Median OS for patients with KRAS mutation was 15 mos vs 23 mos with WT KRAS (log rank p=.0301). Factors associated with poor survival included increased PCI (p=.0502), CC score of 2 (p=.0977), and Clavien classification of IIB or worse (p=.0006). KRAS mutations remained associated with poor survival after adjusting for CC and PCI (p=.0153). Conclusions: KRAS mutations were found in half of CRC carcinomatosis pts selected for CRS/HIPEC where mutational analysis was performed and were associated with worse OS compared to pts with WT KRAS.

P117

Research for Reprogramming of Cancer Cells by Micro RNAs S. Miyazaki,* H. Yamamoto, N. Haraguchi, J. Nishimura, T. Hata, I. Takemasa, T. Mizushima, H. Ishii, Y. Doki, M. Mori. *Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.*

Introduction By introducing four transcription factors (Oct3/4, Sox2, C-Myc, and Klf4) into cancer cells, induced pluripotent cancer (iPC) cells were successfully generated. Although differentiated iPC cells displays a low malignant feature, safety problem exists in the clinical application. This study is conducted to demonstrate whether mature miRNAs, that are supposed not to be integrated into the host genome, can reprogram cancer cells, and induce low malignancy. Methods The mature miRNAs, mir-302s, and 369s are used to reprogram cancer cells led. Proliferation assay and MTT assays were performed to examine cytotoxicity by 5-fluorodeoxyuridine (5-FU) in reprogrammed cells. Result The transfection of microRNAs was performed three times at 48h intervals. Thirty days after transfection, we observed the colonies that showed ES cell like morphology. The analysis of RT-PCR showed that the colonies cells expressed undifferentiated ES cell-marker genes including NANOG, OCT3/4 and SOX2. To evaluate the malignant feature of the reprogrammed cancer cells, we examined proliferation assays and MTT assays. Proliferation assays showed that growth of the reprogrammed cancer cells significantly decreased compared with negative control and parental cells ($n = 6$, 72h: $p = 0.021$, 96h: $p = 0.034$, Wilcoxon rank test). The MTT assay showed that the reprogrammed cancer cells acquired higher sensitivity to 5-FU significantly than negative control ($n = 11$, $p = 0.003$, Wilcoxon's rank test). To determine tumorigenic properties in vivo, the reprogrammed cancer cells and parental cells were injected subcutaneously into dorsal flanks of NOD/SCID mice. Twenty-eight days after injection, the tumor volume of reprogrammed cancer cells was significant smaller from that the parental cells ($p < 0.01$, Wilcoxon's rank test). Conclusion This study showed the reprogramming of cancer cells through the transfection of mature miRNAs increased chemo-sensitivity, and decreased cell proliferation and tumorigenic potential. The reprogramming of cancer cells might to be a new cancer therapy.

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Disparities in the use of Pre-Operative Radiation and Sphincter Preservation among California Rectal Cancer Patients A.W. Chae,* A.D. Yang, R.J. Canter, R.J. Bold, V.P. Khatri, S.R. Martinez. *General Surgery, UC Davis Health System, Sacramento, CA.*

Introduction: Disparities in health care have been documented in several malignancies. We hypothesized that non-white rectal cancer patients would be less likely to receive neoadjuvant therapy (NeoTx) and sphincter preservation (SP) relative to their white counterparts. Methods: We identified patients diagnosed with invasive rectal cancer in California from 1988 through 2009 in the Surveillance, Epidemiology, and End Results database. To examine the use of NeoTx, a subset of patients with T3-T4 tumors or node-positive disease with any T stage were studied. Patients were categorized by race/ethnicity. Preoperative radiation was used as a surrogate for NeoTx. Odds ratios of the likelihood of undergoing SP or receiving NeoTx were calculated using multivariate logistic regression models. Results: Among 19,815 rectal cancer patients, 19,567 (98.7%) had information on SP status. In all, 13,875 (70.9%) underwent SP. In addition, 12,048 rectal cancer patients had T3-T4 tumors or node-positive disease with any T stage and met indications for NeoTx. Of these, 4,350 (36.1%) underwent pre-operative radiation. On multivariate analysis, Asian race/ethnicity predicted the use of SP (OR 1.21, CI 1.09-1.35; p=0.001). Additional factors predicting SP included age ≥ 80 years and female sex. Hispanic race/ethnicity predicted a decreased likelihood of SP (OR 0.76, CI 0.69-0.84; p<0.001). Other factors predicting less SP were advancing T stage, N2 and NX stage, and increasing tumor size. Use of NeoTx was not predicted by any race/ethnicity. Factors predicting use of NeoTx were unknown tumor grade, T3 and T4 tumors, and N1 disease. Decreased use of NeoTx was predicted by Asian (OR 0.74, CI 0.65-0.85; p<0.001), black (OR 0.67, CI 0.54-0.83; p<0.001) and Hispanic (OR 0.77, CI 0.67-0.88; p<0.001) race/ethnicity. Additional factors predicting less use of NeoTx were increasing age, female sex, grade II and grade III tumors, advancing tumor size, and N2 and NX nodal stages. Conclusions: There are racial/ethnic disparities in the use of SP and NeoTx for rectal cancer treatment. Future research should address their influence on patient satisfaction and survival.

P119

Expression of GAB2 in Human Colorectal Cancer T. Matsumura,[1]* R. Uchi,[1] H. Ueo,[1] M. Ishibashi,[1] G. Sawada,[1] Y. Takahashi,[1] K. Mima,[1] J. Kurashige,[1] S. Akiyoshi,[1] T. Sudo,[1] K. Sugimachi,[1] K. Shibata,[1] M. Mori,[2] K. Mimori.[1] *1. Kyushu University Beppu Hospital, Beppu, Japan; 2. Osaka University Graduate School of Medicine Department of Gastroentelogical Surgery, Suita, Japan.*

INTRODUCTIN: The scaffolding adaptor protein GAB2 (GRB2-associated binding protein2) located on 11q14.1. was known its interaction with PI3K,which is important for Fc receptor signaling in mast cells. And as an oncogenic protein GAB2 was commonly overexpressed in several human malignancies, including malignant melanoma, breast cancer and ovarian cancer. Recent study provided that GAB2 plays a critical role in proliferation and migration of mammary tumor through Shp2 dependent pathway. However, the roles of GAB2 in colorectal cancer are unknown. METHODS: In this study, we analyzed the expression of GAB2 in colorectal frozen tissue samples from 156 patients with colorectal cancer, using quantitative real-time-PCR. We assessed the correlation between expression of GAB2,and clinic pathological features and prognosis. RESULTS: We found that the expression of GAB2 in tumor colorectal tissues was significantly higher than in normal colorectal tissues (p value=0.0179). Furthermore, high expression of GAB2 were associated with malignant clinicopathologic potential such as lymph invasion (p=0.0002), venous invasion (p value=0.0108) and liver metastasis (p value=0.0088). And the survival rate of the patients who were high for GAB2 expression was significantly lower than that of patients with low expression of GAB2 (p value =0.0088) . CONCLUSIONS: Expression of GAB2 might has any roles in the growth and metastasis of colorectal cancer and contribute to progression and prognosis in patients with colorectal cancer.

P120

Short- and Long-term Results of Intersphincteric Resection for Very Low Rectal Carcinoma M. Takawa,* T. Akasu. *National Cancer Research Center Hospital, Tokyo, Japan.*

BACKGROUND: Intersphincteric resection has recently been considered as an alternative option to avoid permanent colostomy for selected patients with very low rectal carcinoma. However, with intersphincteric resection, there is a potential risk of increasing short- and long-term morbidity and mortality. OBJECTIVE: To evaluate short- and long-term morbidity and mortality of intersphincteric resection for patients with very low rectal cancer, retrospective clinicopathologic analysis of prospective data registry was done. METHODS: Between 1997 and 2012, 186 patients with cT1-to-cT3 rectal adenocarcinoma below 5 cm from the anal verge underwent total mesorectal excision with intersphincteric resection. All patients underwent curative-intent surgery. Of them, 151 patients had open surgery, and 35 laparoscopic surgery. Four patients received neoadjuvant chemoradiotherapy and 43 received adjuvant chemotherapy. RESULTS: There were 138 men and 48 women with a median age of 55 (range 22-79) years. Median distance between tumor and the anal verge was 3 (range 1-5) cm. There were 1 ypT0, 51 pT1, 1 ypT1, 64 pT2, 1 ypT2, 67 pT3 and 1 ypT3 tumors. One patient had disease categorized as stage 0, 85 as stage I, 31 as stage II, 64 as stage III, and 5 as stage IV.

Histopathologic radial and distal margins were negative for 183 patients, but 3 patients had positive margins. Short-term morbidity and mortality of the 186 patients were 26% and 0.5%, respectively. Eleven patients underwent emergency operation and 8 patients had permanent stoma due to complication. Fifteen patients (8%) developed anastomotic leakage. Median follow-up of the all patients was 5.0 (range 0-12) years. Five-year overall and relapse-free survival rates of the 186 patients were 90% and 78%, respectively. The rates of local and distant recurrence of the 186 patients were 6% and 16 %, respectively. CONCLUSION: This study suggested that intersphincteric resection is safe procedure for selected patients with cT1-to-cT3 rectal cancer below 5 cm from the anal verge in terms of short- and long-term morbidity and mortality.

P121

The Influence of Age on Outcomes of Laparoscopic Colorectal Surgery for Cancer: Comparative Analysis of 10-Year Experience

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Introduction: Laparoscopic colorectal surgery (LCS) for cancer has been shown to offer shorter hospital stay, less narcotic pain requirement, lower wound complications and faster recovery when compared with open approach. These characteristics are particularly beneficial for older and high-risk individuals. In this study, we describe our 10-year experience of LCS for cancer and compare the surgical outcomes from different age groups. Methods: A retrospective review of 500 consecutive patients who underwent laparoscopic colorectal operation for colorectal cancer between 1999 and 2009 was performed. Patients were classified into 2 groups based on age, ≤70 years (Group A) and >70 years (Group B) at the time of the operation. Operative variables, postoperative complications, and 30-day mortality were compared. Results: A total of 237 patients with mean age of 57.7 years (range: 18-70) were included in group A and 263 patients with mean age of 79.7 years (range 71-95) were included in group B. There were no significant differences with regards to gender and type of operations performed. Of the operative variables, the average length of procedure was comparable between group A and B (127.7 vs 118.8 minutes, respectively, p>.05), while the younger group had slightly higher operative blood loss compared with the older group (185.8 vs 154 ml, p=.016). Six (2.53%) patients in group A and 13 (4.94%) patients in group B required open conversion. Postoperative bleeding (3.8%) and leak (0.7%) rates were comparable between the 2 groups. The older group was found to have higher cardiac-related events (6.84% vs 3.8%, p<.05), major pulmonary complications (1.9% vs 0%), venous thromboembolism (1.9% vs 0%), and mortality (3% vs 0%). The older group required longer hospital stay (5.41 vs 4.42, p>.05) days. The average number of lymph nodes harvested was comparable between group A and B (22.04 vs 21.5, p>.05). Conclusions: Laparoscopic colorectal surgery for cancer results in comparable operative outcome variables regardless of patient's age. Postoperative cardiopulmonary complications are higher, however still acceptable in older individuals.

P122

Adjuvant Chemotherapy Improves Survival of Elderly Patients with Stage III Colorectal Cancer

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INTRODUCTION: Controversy remains regarding the utility of adjuvant chemotherapy in the elderly population after curative resection for stage III colorectal cancer (CRC). We sought to assess the efficacy of adjuvant chemotherapy (AC) post resection in an elderly population with stage III CRC in a single regional tertiary referral centre. METHODS: CRC patients treated with curative surgery from 7/99 to 12/05 were identified from a prospective database. Oncological outcome and toxicities were compared in patients under (adult) and over the age of 70 (elderly). Kaplan Meier survival curves were constructed; overall (OS) and recurrence free survival (RFS) were compared by log rank. Categorical variables were compared with the Chi-square test (SPSS 19.0). RESULTS: We identified 149 patients of which 70 were elderly. Compared to adult patients, fewer elderly received AC (61.4% vs 94.9%, p<0.001). Two (3%) of the elderly received oxaliplatin in addition to 5FU, compared to 20% of the adult group (p<0.001), hence we cannot comment on its utility. There were more CTCAE grade 3 (13 vs 5) toxicities observed in the adult group with more grade 4 in the elderly (0 vs 4, p=0.024). The majority of the toxicities in the elderly were gastrointestinal (11 vs 3), versus hematological in the adults (9 vs 4, p=0.02). There was no difference in those requiring dose reduction, omission or discontinuation of chemotherapy. We found no difference in RFS or OS (77.2% vs 84.3%) between adult and elderly patients with or without AC (p>0.05). We observed a significantly improved OS (p<0.001) and RFS (p<0.001) in elderly patients receiving AC in addition to resection compared to elderly who did not receive AC. ECOG performance status and ASA classification were equivalent. CONCLUSIONS: We found that AC in addition to curative surgery improved the relapse free and overall survival in elderly patients with stage III colorectal cancer. The profile of toxicities was different in the elderly; however the proportion discontinuing or attenuating AC was equivalent. AC should be considered in addition to surgery for elderly patients with stage III CRC.

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Clinicopathologic Characteristics and Prognostic Predictors of Survival in Patients with Diffuse Malignant Peritoneal Mesothelioma (DMPM) treated with Cytoreductive Surgery (CS) and Perioperative Intraperitoneal Chemotherapy: A Single Institution's Experience

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Introduction: - Diffuse Malignant Peritoneal Mesothelioma (DMPM) is an aggressive disease with a poor prognosis. Our aim was to analyze the trend in treatment paradigms, and clinicopathologic characteristics and prognosis of DMPM in our cohort of patients over a 23 year period. Methods: - A retrospective analysis of a prospectively maintained database for all patients treated for DMPM from 1989-2012. This period was divided into two time frames 1989-2003 and 2004-2012 reflecting the evolution of our treatment paradigm. Results: - Of 213 patients in our study there were 119(55.9%) males vs. 94(44.1%) females. The mean age of presentation was 49.1 years, (range of 16 – 79 years). Grouped by age-specific groups; 101(47.4%) were between 16-49 years vs. 112(52.6%) who were ages 50-79 years. For the period 1989 - 2003 there were a total of 109(51.2%) patients vs. 104(48.8%) for years 2004-2012. Overall DMPM survival was 58.7%, median survival and follow-up time was 63 and 36.3 months respectively. Three and 5 year survival was 56% and 32% respectively. Median survival time for the period 1989-2003 was 42 months vs. 77 months for 2004- 2012 (p= 0.05). Median survival time for the various age-groups were 82 and 43 months respectively for 16-49 years, and 50-79 years (p= 0.01). The median survival time for males was 42 vs. 82 months for females (p=0.01). Patients who had a completeness of cytoreduction (CC) score of 0 (no residual disease) had a median survival of 147 months vs. 132.1, 71.6, and 27.9 months respectively for patients who had a CC-1:-<0.25 cm, CC-2:-0.25-2.5cm, and CC-3:->2.5cm residual tumor (p=0.000). A significant independent predictor of a shorter survival in multivariate analysis was a high CC status HR 3.8 (95% CI 2.2 – 6.5, p< 0.000). Gender, age, time period did not achieve significant status. Conclusion: - Advanced age and male gender may contribute to the poor prognosis associated with DMPM. An independent predictor for an improved overall survival includes completeness of cytoreduction

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Postoperative Complications Affect Long-Term Outcome after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Cancer Peritoneal Carcinomatosis

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INTRODUCTION Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective but potentially morbid treatment option for colorectal cancer peritoneal carcinomatosis (CRCPC). Better survival results correlate with complete surgical cytoreduction and limited peritoneal involvement, but additional prognostic factors are still poorly known. The negative impact of postoperative complications on long-term outcome has been reported in various tumors, but it has never been assessed

in CRCPC after CRS and HIPEC. METHODS We reviewed a bi-institutional prospective database of 93 patients treated by CRS and HIPEC with cisplatin and mytomicin-C. The impact of major operative morbidity (grade 3-5 according to the National Cancer Institute Common Terminology Criteria v.4.0) on disease-specific survival was assessed by multivariate analysis; 38 clinicopathological control variables were tested. The extent of peritoneal involvement was scored by peritoneal cancer index (PCI). RESULTS Mortality and major morbidity were 3.2% and 24.5%. Reoperation rate was 7.4%. Median follow-up was 31.6 months (95% confidence interval (CI) 24.3-38.9). Median and 5-year overall survival were 33.0 months (95%CI 17.2-48.8) and 40.5%. Five-year disease-specific survival was 16.8% (median 19.6 months; 95%CI 15.9-23.1) for patients who experienced major complications, and 58.0% (median 63.0; 95%CI not evaluable) for those who did not (P=0.042). Major morbidity retained adverse prognostic significance even after multivariate analysis (hazard rate (HR) 2.4; 95%CI 1.2-4.8; P=0.016), along with WHO performance score >0 (P=0.036), PCI >18 (P=0.035) and completeness of cytoreduction (P=0.048). Longer operative time (P=0.011) and PCI >18 (P=0.025) were independent predictors of major morbidity. CONCLUSIONS The avoidance of major complications, by refining surgical technique and patient selection, is crucial because it impacts long-term survival. This suggests that CRS with HIPEC should be performed in specialized centers to give the patient the best possible condition to reach long-term survival.

P125

Increasing Incidence Rates for Anal Squamous Cell Cancer in the United States, 1980-2009 L. Eberly, C. Wiggins, I. Nir, K.T. Morris, J. Russell, A. Rajput.* *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Anal squamous cell carcinoma (SCC) is a rare neoplasm, but it results in significant morbidity and mortality. The aim of this study was to characterize the trends of anal SCC in the United States between the years 1980-2009. Methods: Eligible subjects were identified from existing records in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The study included incident cancers of the anus, anal canal, and anorectum (ICDO-3 anatomic site codes C21.0-C21.2 and C21.8) that were diagnosed among residents of nine core areas of the SEER Program during the time period 1980-2009. The study was restricted to squamous cell histologies (ICDO-3 histology codes 8050-8099) of malignant behavior (ICDO-3 behavior code of 3). Average annual age-adjusted incidence rates were calculated by the direct method using the United States 2000 standard population. Ninety-five (95) percent confidence intervals for the incidence rates were calculated using the Tiwari adjustment. Temporal trends in incidence rates were assessed with joinpoint regression techniques. Results: Incidence rates for anal cancers in the United States more than doubled during the period 1980-2009 (see Table). By joinpoint regression, a linear increase in anal cancer incidence rates was observed during the study period with an Annual Percent Change (APC) of 4.6 percent ($p<0.01$) for all races and both sexes-combined. Incidence rates were consistently greater for women than men, however, the increase in incidence rates was greater for men (APC=5.4 percent, $p<0.01$) than for women (APC=4.3, $p<0.01$). Similar trends were observed among both whites and blacks. Conclusions: Anal cancer is a relatively rare disease. Incidence rates, however, for this disease have increased dramatically in the United States over the last three decades. Correlation of this increased incidence with HPV infection remains to be determined.

Anal Cancer - Average annual age-adjusted incidence rates per 1,000,000 (US 2000 Standard)

Race	Sex	Time Period of Diagnosis		
		1980-1989	1990-1999	2000-2009
		Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
All Races (n=5,846)	Both Sexes	4.74 (4.44-5.06)	6.99 (6.65-7.34)	11.61 (11.21-12.01)
	Male	3.61 (3.22-4.04)	6.02 (5.57-6.51)	10.13 (9.59-10.70)
	Female	5.53 (5.09-6.00)	7.63 (7.15-8.13)	12.75 (12.18-13.33)
Whites (n=5,015)	Both Sexes	4.86 (4.53-5.21)	7.26 (6.89-7.65)	12.38 (11.92-12.85)
	Male	3.73 (3.31-4.20)	6.10 (5.59-6.63)	10.34 (9.73-10.98)
	Female	5.62 (5.14-6.13)	8.08 (7.55-8.65)	14.10 (13.43-14.79)
Blacks (n=678)	Both Sexes	5.97 (4.79-7.35)	8.57 (7.35-9.93)	13.72 (12.36-15.18)
	Male	4.84 (3.23-6.94)	9.10 (7.25-11.28)	15.29 (13.22-17.59)
	Female	6.91 (5.24-8.90)	7.99 (6.42-9.82)	11.99 (10.28-13.89)

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The Requirement for Freshly Isolated Human Tumor Cells for the Study of Colorectal Cancer Stem Cells S. Bellister,* F. Fan, F. Tozzi, J. Lu, L. Xia, R. Bhattacharya, Y. Zhou, X. Ye, L. Ellis. *University of Texas MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: Reliable methods for the isolation of an enriched cancer stem cell (CSC) population in colorectal cancer (CRC) may provide new approaches for the identification of therapeutic targets. There is no consensus regarding the best methods to isolate a CRC tumor cell population enriched for CSCs. The goal of this study was to determine the utility of various CSC markers in both established cell lines and freshly isolated patient-derived tumor xenografts in order to validate methods of CSC isolation. METHODS: Established human CRC cell lines (HCT116, HT29, SW480) and three freshly isolated CRC cell lines were studied. Freshly isolated cell lines were generated by first injecting CRC cells derived from clinical specimens into nude mice. Xenografted tumors were resected and FAC-sorted to isolate human cells. These cells were FAC-sorted for CD133, CD44, and ALDH activity. Tumorsphere formation and in vivo dilutional and serial tumorigenicity studies were done to validate methods for CSC enrichment. RESULTS: Using established human CRC cell lines, none of the markers studied could be used to enrich for the CSC population as assessed by sphere formation or tumor initiating capacity; this suggests that cells grown in culture for long periods of time lose their hierarchy. In the freshly isolated CRC cells, CD133 and CD44 were unable to enrich for CSC-ness. In contrast, freshly isolated CRC cells with high ALDH activity formed spheres whereas cells with low ALDH activity did not. In validation studies, freshly isolated cells from patient-derived xenografts with high ALDH activity demonstrated enhanced tumorigenic capacity in murine models. Furthermore, the tumorigenicity of ALDH high cells was maintained after serial passage of cells harvested from tumors generated by ALDH high cells, while ALDH low cells did not form tumors. CONCLUSION: CRC cells from patient-derived tumor xenografts can be used to study CSC properties using ALDH activity as a marker. In contrast, CD44 and CD133 are not reliable markers for enriching for the CSC population from established cell lines or patient xenografts. Established CRC cell lines should not be used to study CSC biology.

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WITHDRAWN

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KRAS Mutation is Associated with Favorable Prognosis among Patients with Appendiceal Carcinomatosis P. Wagner,* D. Caba Molina, C. Huynh, N. Kulkarni, M.P. Holtzman, A.H. Zureikat, S.A. Ahrendt, J.F. Pingpank, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: KRAS mutation status has been widely studied as a pathogenic and predictive factor in metastatic colorectal cancer. However, little is known regarding the role of KRAS mutation in the pathogenesis and prognosis of appendiceal cancer. The purpose of this study was to determine the prevalence of KRAS mutation and define its clinicopathologic significance in a population of patients being treated for appendiceal caricnomatosis. Methods: KRAS mutation status was determined in 159 patients undergoing attempted cytoreductive surgery and heated intraperitoneal chemotherapy for appendiceal carcinomatosis. Patients were stratified on the basis of KRAS mutation status in order to assess for correlation with patient and tumor characteristics, as well as oncologic outcomes (overall and progression-free survival). Results: KRAS mutation was highly prevalent among patients with appendiceal carcinomatosis, being present in 95 cases (60%). Most mutations were in codon 12 (86%), with the remainder being codon 13 mutations. KRAS-mutated tumors were less likely to be high grade (33% vs. 55%, p=0.009) or to contain signet cells (5% vs. 36%, p<0.0001), and more likely to be associated with elevated serum CEA level (67% vs. 35%, p=0.002). With limited follow-up (median, 21.6 months), a survival advantage was apparent among patients with KRAS-mutated tumors (12-month survival 90.5% vs. 83.1%, log-rank p<0.05; number-at-risk, 73 and 40, respectively). No difference in patient age, gender, disease volume, node status or time-to-progression was observed on the basis of KRAS mutation status. Conclusions: KRAS mutation status characterizes a subset of appendiceal carcinomatosis patients with a more favorable prognosis. Future studies will determine whether KRAS status can be incorporated into existing treatment algorithms in order to improve selection of patients in whom aggressive surgical therapy (i.e., CRS-HIPEC) may be appropriate.

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Systematic Review of Outcomes of Patients Undergoing Resection for Colorectal Liver Metastases in the Presence of Extra-hepatic Disease M. Hwang, D. Green, R.T. Groeschl, S.G. Pappas, J.P. Thomas, B. Erickson, T. Gamblin, K.K. Turaga.* *Surgery, Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Patients with extrahepatic metastases are being increasingly considered for hepatic resection. We conducted a systematic review to examine the survival data of patients undergoing hepatic resection in the setting of resectable extrahepatic disease. We hypothesized that the survival for this group of patients was dependent on the location of extra-hepatic disease. Methods: Our review was prospectively registered with the PROSPERO Registry (CRD42012002827). A search strategy was developed using MESH headings and terms e.g.(colorectal cancer) AND (liver resection). We included all articles published after 2003 . Evidence synthesis and quality score analysis was performed using standard evidence tables with logic checks. Results: Of 4856 papers, we included1535 articles for preliminary review. After applying our inclusion criteria, we included 96 articles, of which 79 also reported survival data and form the basis of this paper. There were a total of 31489 patients undergoing liver resection, with 4632 of them undergoing liver resection in the presence of extrahepatic disease. The overall median survival of these patients after surgery was 30.5 months, with 1-year, 3-year, 5-year, and 10-year overall survival of 86%, 40%, 28%, and 22%, respectively. Of all the sites of extrahepatic metastases, the lung had the most favorable prognosis, with a median survival of 41 months and a 5yr survival of 39%. Conclusions: Selected patients undergoing resection of hepatic and extrahepatic disease (especially pulmonary metastases), in conjunction with multimodality therapy have better survival than previously reported. Prospective randomized data may eliminate the publication bias inherent in our systematic review.

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Pretreatment Albumin/Globulin Ratio as Predictors of 4-year Cancer-related Mortality in Colorectal Cancer Patients B. Azab,* S. Vonfrolio, W. Lu, S. Bloom. *Surgery, Staten Island University Hospital, Staten Island, NY.*

Aim of this study: Our aim in this study was to the value of the pretreatment Albumin/ globulin ratio (AGR) to predict the long term mortality in CRC patients with normal serum albumin (i.e. > 3.5gm/dl). Methods: We have used our data base of CRC patients diagnosed between 2005 and December 2009. Patients were included if they had comprehensive metabolic panel (CMP) before treatment (surgery or chemotherapy) and albumin level were >3.5gm/dl. Two independent physicians have reviewed the charts for the demographic, presentation, laboratory, pathological, management and outcome variables. The primary variables were WBC parameters (serum total proteins, albumin, calculated AGR). Patients were divided into three equal tertiles according to their pretreatment AGR [1st AGR tertile (AGR > 1.5) = 83 patients, 2nd AGR tertile (AGR 1.5-1.3) = 84 patients and the 3rd AGR tertile (AGR<1.3) =88 patients]. Similarly, patients were divided to albumin tertiles [albumin >3.9 (95 patients), albumin 3.9-3.8(76 patients) and albumin 3.7-3.6(84 patients). The primary outcomes: cancer-specific mortality which was obtained from our cancer registry data base. Results: Out of 652 consecutive CRC patients, we had 255 patients with pretreatment CMP and albumin >3.5gm/dl. The 1st AGR tertile had a significant lower 4-year mortality compared to the 2nd and 3rd AGR tertiles (0% vs. 13% and 15%, p<0.0001 according to Fisher's exact two-tailed test). Likewise, the lowest albumin tertile had a lower 4-year mortality compared to the higher albumin tertiles (6.3 vs. 6.5% vs. 16.7%/, p=0.02 and p=1). Interestingly, highest globulin tertile had higher mortality than the lowest tertile (2% vs. 18%, p<0.0001). (Figure 1) Conclusion: AGR was a strong predictor of long-term cancer specific survival among colorectal cancer patients. We noticed superiority of AGR to albumin in predicting the overall survival in CRC patients. This finding was found in patients with normal albumin. This suggests that AGR is possible inflammatory predictor of cancer progression.

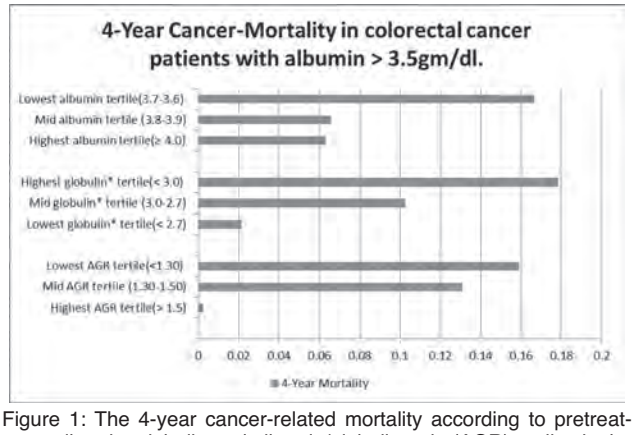

Figure 1: The 4-year cancer-related mortality according to pretreatment albumin, globulin and albumin/globulin ratio (AGR) tertiles in the colorectal cancer patients.

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Identification of Novel Tumor Suppressor Gene HOPX (Homeobox Only Protein), +4 Quiescent Stem Cell Marker, Elucidated Critical Targets of EphA2 and Cyr61 in Human Cancers K. Yamashita,* H. Katoh, A. Ooki, M. Waraya, H. Kawamata, M. Watanabe. *Surgery, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan.*

(Background) Cytosine DNA methylation of promoter CpG islands plays a critical role in human cancer. Pharmacological unmasking microarray (PUM) discovered many such genes, which are herein tabulated. HOPX is of particular interest due to its prognostic relevance, prevalent tumor suppressor function, and recent discovery as +4 quiescent stem cell marker for colorectal mucosa cell. (Aim) To elucidate mechanistic insight of HOPX tumor suppression to identify oncogenic targets in GI cancer. (Materials and Methods) PUM methods identified novel methylation genes. Scores to judge their sig-

nificance depend on frequency and specificity of hypermethylation in human primary GI cancers (esophageal, gastric, colorectal, and pancreatic cancers). Clinicopatholgoical analysis including multivariate assay was done for HOPX. HOPX was evaluated for functional relevance in proliferation, apoptosis, invasion, tumorigenesis,and angiogenesis. Expression profiles by microarray elucidated critical target candidates. (Results) (1) Tabulated genes were PGP9.5, NEFH, DCC, HOPX, Reprimo, NMDAR2B/2A that were specifically methylated in human cancers (AUC>0.7). (2) Prognostic relevance of HOPX methylation was confirmed both in learning set and validation set of esophageal (n=50 and 170), gastric (n=80 and 90) and stage III colorectal cancer (n=170). (3) Pancreatic cancer is uniquely defective for HOPX expression and pharmacological unmasking failed to reactivate its expression differently from other GI cancer. (4) HOPX transfection suppressed aggressive tumor traits commonly in GI cancers. (5) HOPX remarkably inhibited onco-targets of EphA2 and Cyr61, and their correlation with HOPX expression/methylation status was validated for EphA2 and Cyr61 expression in primary cancers. (Conclusion) Our present findings strongly supported hypothesis that HOPX is a critical tumor suppressor gene, and its epigenetic silencing or defective constitutive expression represent tumor aggressive phenotypes at least through stabilization of critical tumor stimulators of EphA2 and Cyr61.

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Tissue-penetrative Targeting of Peritoneal Metastases K.N. Sugahara,[1]* T. Teesalu,[1] V. Kotamraju,[1] A.M. Lowy,[2] E. Ruoslahti.[1] *1. Cancer Research Center, Sanford-Burnham Medical Research Institute, La Jolla, CA; 2. University of California, San Diego, San Diego, CA.*

INTRODUCTION: Intraperitoneal chemotherapy suffers from poor drug penetration and is potentially efficacious only upon near-complete cytoreductive surgery. iRGD is a peptide that targets and penetrates tumors through circulation and direct contact with tumor tissue. Here, we tested the utility of iRGD in visualizing disseminated peritoneal tumors and enhancing tumor drug penetration. METHODS: iRGD was injected intraperitoneally into peritoneal tumor mice, and the accumulation of iRGD into tumor nodules was evaluated with imaging and microscopy. Under an IRB approved protocol, iRGD was tested on fresh tissue following cytoreductive surgery in ex vivo tumor penetrating assays. RESULTS: Fluorescein-labeled iRGD (FAM-iRGD) efficiently accumulated into disseminated peritoneal tumors of various sizes, up to over one centimeter. FAM-iRGD penetrated all three tumor types tested, colon, gastric, and ovarian cancer. The penetration was mainly through direct contact with the tumors as evidenced by the fact that peritoneal tumors showed much stronger signals of FAM-iRGD than subcutaneous tumors that were only accessible through the circulation. Co-administration of iRGD and fluorescent dextran resulted in tumor-specific accumulation of dextran, strongly suggesting that mixing iRGD into intraperitoneal chemotherapy regimens could significantly enhance tumor penetration and efficacy of the drugs. CRGDC, a tumor-targeting peptide with no tissue penetration properties, had no effect on dextran accumulation into the tumors. This finding is in line with the known ability of iRGD to initiate a bulk transport pathway through tumor tissue to promote tumor penetration of co-applied compounds. iRGD efficiently penetrated fresh human peritoneal tumor samples as large as three centimeters in ex vivo assays, indicating the translational potential of the iRGD technology. CONCLUSION: iRGD delivers compounds attached to iRGD and even those simply co-applied with iRGD deep into peritoneal tumors independent of circulation. iRGD may significantly improve intraoperative visualization of disseminated peritoneal tumors to facilitate cytoreduction, and potentiate intraperitoneal chemotherapy by promoting tumor penetration of co-applied drugs.

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Adiponectin Promotes a more Aggressive Colon Cancer Phenotype Associated with Activation of ERK1/2 and AMPK Pathways W. Clark,* A. Elahi, L. Humphries, D. Coppola, J. Hernandez, D. Shibata. *Moffitt Cancer Center, Tampa, FL.*

Introduction: Adiponectin (APN) is an adipokine that has purported antidiabetic and anti-atherosclerotic properties and may play a role in the link between obesity and cancer. However, its impact on carcinogenesis remains controversial. We sought to investigate the impact of APN on colon cancer (CC) behavior. Methods: Gene expression was analyzed using the Affymetrix 2.0 GeneChip. Expression of APN and its main receptor, AdipoR1 (AR1) were evaluated using Western Blot. Knockdowns were performed using siRNA. Effects on proliferation, invasion, and anchorage-independent growth were measured by MTT, modified Boyden chamber and soft agar assays respectively. Results: By microarray profiling of 2 independent patient datasets, APN was identified among the most highly upregulated genes (+3.1 and +2.7 fold) in metastatic (n=22 and 40) vs non-metastatic (n=26 and 17) CCs. Antibody staining of CC tissues demonstrated a tendency towards more frequent expression of APN (p=NS) and AR1 (p=0.03) in advanced stage tumors. APN and AR1 protein expression was confirmed in multiple CC cell lines. Treatment of the HCT116 line with full length exogenous APN (1ug/ml) resulted in a significant increase in proliferation ($p<0.001$) and a trend towards increased invasion (p=0.08) as compared to untreated cells. Knockdown of APN resulted in reductions in proliferation (p=0.04) and invasion ($p<0.001$) but not growth in soft agar. Knockdown of AR1 alone yielded an attenuation in invasion ($p<0.001$) but not proliferation nor growth in soft agar. However, combined knockdown of APN+AR1 resulted in significant synergistic reductions in proliferation ($p<0.0001$), invasion ($p<0.001$) and growth in soft agar ($p<0.04$) as compared to nonsense controls. Stimulation by exogenous APN induced the activation of ERK1/2 and AMPK. Conclusions: APN is differentially overexpressed in primary CCs with metastatic capacity. Despite known favorable metabolic systemic effects, APN via its main receptor, AR1, promotes a more malignant behavior which may be mediated in part, by the ERK and AMPK pathways. The APN signaling pathway warrants further investigation as a potential therapeutic target in CC.

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Adequacy of Lymphadenectomy During Laparoscopic Colorectal Operation for Cancer: A Decade Experience from A Major Subur-ban Tertiary Center I. Sucandy,* A. Yushuva, S. Fassler, S. Kim, M. Zebley. *Surgery, Abington Memorial Hospital, Abington, PA.*

Background: Lymph node harvest of ≥12 has been adopted as a marker for adequacy of colorectal cancer resection. Type of operation, specimen length and age have been reported to be independent predictors for the number of retrieved lymphnodes, while gender, ethnicity, and operative approach had no influence. Many of the previous studies were performed with limited number of patients. We designed a study to evaluate our 10-year experience on the adequacy of lymphadenectomy during laparoscopic colorectal cancer operation and its potential predictors. Methods: A retrospective review of 500 patients who underwent laparoscopic colorectal cancer operations between 1999 and 2009 was performed. Patients were classified into 2 groups based on the number of lymphnodes retrieved (Group A : <12 nodes and GroupB : ≥12 nodes). Results: A total of 65 patients were included in group A with average retrieved lymphnodes of 8.2, and 435 patients were included in group B with average retrieved lymphnodes of 23.8. When Group A and B were compared demographically, the average age (69.3 vs 69.2 years, respectively) and gender distribution were comparable. Of the operative variable, Group A had a higher operative time (123.4 vs 120.6 minutes, p=2.39), estimated blood loss (181.9 vs 165.3 ml, p=0.99), and length of stay (6 vs 4.9 days, p=0.26). Type of operation correlated with number or lymphnodes retrieved [total colectomy resulted in highest number of lymphnodes (average 40.3 nodes) and proctectomy resulted in lowest number of lymphnodes (average 14.7 nodes)]. Operative approach (laparoscopic vs open) did not predict the number of lymphnodes retrieved (21.7 vs 21.4, p<.05 respectively). Postoperatively, the rate of bleeding, intra-abdominal infection, intestinal ileus were comparable. Conclusions: Type of operation, but not the approach correlates with the number of lymphnode harvested. Demographic factors such as age and gender did not predict adequacy of lymphadenectomy. Cases with <12 node harvested were potentially more technically challenging, reflected by higher operative time, blood loss, and longer hospital stay

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Impact of Tumor Histology on the Efficacy of Surgical Therapy for Peritoneal Carcinomatosis of Colorectal Origin J.H. Winer,* H.A. Choudry, J.F. Pingpank, A.H. Zureikat, M.P. Holtzman, L. Ramalingam, H.J. Zeh, D.L. Bartlett, S.A. Ahrendt. *Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction Multiple retrospective series and a randomized phase III trial have demonstrated improved median survival and a 20-30% 5 year sur-

vival rate after aggressive cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemoperfusion (HIPEC) for peritoneal carcinomatosis (PC) of colorectal origin, when compared to systemic chemotherapy alone. We sought to determine the impact of tumor histology on oncologic outcomes. **Methods** We reviewed 208 patients with PC of colorectal origin from a prospective database between May 2001 and August 2011. Survival times were determined and compared using the Kaplan-Meier method and two-tailed log-rank test. **Results** Median peritoneal carcinomatosis index (PCI) was 9 (IQR 9) and complete cytoreduction (CC-0/1) was achieved in 168 (81%) patients. Mitomycin C was the drug of choice for chemoperfusion (n=182, 87%), and 23 patients did not receive HIPEC due to incomplete resection, parenchymal metastases, or minimal isolated studding. Histologic subtypes included mucinous adenocarcinoma (n=82, 39%), non-mucinous adenocarcinoma (n=86, 41%) and signet ring cell phenotype (n=30, 14%). 100 (48%) patients had high-grade tumors. Median and 5 year overall survival (OS) were 20m and 25%. Patients with complete CRS (CC-0/1) and those with low PCI scores (PCI ≤ 10) demonstrated significantly improved survival. Patients with signet cells had poor survival (12m vs. 20m, p=0.04), however, complete CRS/HIPEC of these tumors significantly improved OS (17m vs. 2m, p=0.0001). Patients with high-grade tumors had a trend towards worse survival (16m vs. 21m, p=0.1), especially when signet cells were present (12m vs. 18m, p=0.1). Complete CRS/HIPEC (CC-0/1) significantly improved these patients' OS (15m vs. 7m, p=0.001). **Conclusions** Histologic features including signet cells and high-grade morphology adversely impacted oncologic outcomes in patients with PC of colorectal origin. Complete CRS/HIPEC improved survival despite these high-risk features. Effective multimodality therapeutic strategies are essential to reduce tumor burden, allow complete resection and improve survival in patients with colorectal carcinomatosis.

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Increasing Experience with Cytoreduction and HIPEC Enables New Centres to Start Off on a Higher Level A. Kuijpers,[1]* A. Aalbers,[1] S. Nienhuijs,[3] I. De Hingh,[3] R. Wiezer,[2] B. Van Ramshorst,[2] R. Van Ginkel,[4] K. Havenga,[4] H. De Wilt,[5] L. Te Velde,[6] A. Bremers,[5] V. Verwaal.[1] *1. Dutch Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 2. Sint Antonius Hospital, Nieuwegein, Netherlands; 3. Catharina Hospital, Eindhoven, Netherlands; 4. University Medical Centre Groningen, Groningen, Netherlands; 5. University Medical Centre Nijmegen, Nijmegen, Netherlands; 6. VU Medical Centre, Amsterdam, Netherlands.*

Introduction The combination of cytoreduction (CRS) and HIPEC has become the treatment of peritoneal surface malignancies. This complex treatment is known to have substantial morbidity and mortality. Learning curve studies showed a decrease of morbidity. In this study, outcome of CRS and HIPEC was analysed for treatment results between a pioneer institution and institutions which started when education and training was available. Methods The first consecutive 100 CRS and HIPEC procedures of four institutions in the Netherlands were included. Indications for this treatment were peritoneal carcinomatosis (PC) originating from colorectal carcinoma and pseudomyxoma peritonei (PMP). Analysis of operation characteristics, morbidity and completeness of cytoreduction was done to determine the historical learning curve. Furthermore, learning curves within institutions were analysed regarding morbidity and completeness of CRS. Results Four-hundred seventy-two cases were included in the four institutions. In total 327 procedures were performed for PC from colorectal carcinoma and 145 for PMP. The tumour load and the total of resections were larger in the experimental procedures of the first hospital than in the other hospitals. A macroscopic radical resection was reached in 66% of the cases in the first centre and in 86% of the cases in the later centres (75-93% p<0.001). There was a significant association with the rank of the operation and completeness of the CRS. Grade III-V morbidity was higher in the pioneer institution than in the later institutions (OR 3.7, 95% confidence interval 2.3-5.9). Conclusions This study showed that hospitals which started after proper training had a better patient selection. completeness of CRS and morbidity was better in those institutes which started later. Institutions showed a learning curve in CRS in the first 100 procedures. Experience built by the pioneer institution contributed to a higher start off level for new CRS and HIPEC centres.

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WITHDRAWN

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Risk Factors for Positive Radial Margins in North American Rectal Cancer Patients I. Esemuede,* N. Wilkinson, V. Francescutti. *Surgery, Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: A positive radial margin (RM) after rectal resection for cancer is associated with certain tumor and patient characteristics in numerous European studies. The aim of this study is to define those factors in a cohort of North American patients treated at a national cancer center. Methods: Data on patients who were treated for rectal cancer at a United States national cancer center between the years 2005 and 2011 were collected and prospectively entered into a national database. There were 270 patients, of which 193 had potentially curative major surgical resections for rectal cancer. Results: The median age of the cohort was 59.2 years, and were 60% male. The majority received chemotherapy and/or radiation therapy preoperatively or postoperatively. There were 27 patients who had positive RM (RM+), and 160 patients with negative RM (RM-). On univariate and multivariate analysis, a positive margin postoperatively was associated with male gender (p=0.0366 and 0.017, respectively), T stage(p=0.0482 and 0.058), and perineural invasion (p=0.0018 and 0.006). On univariate analysis, RM+ was associated with decreased survival (p=0.014), but not on multivariate analysis. Presence of lymph node metastasis (p=0.199), LVI (p=0.966), and type of surgery (p=0.8506) were not associated with circumferential margin positivity. Five year overall survival (OS) was better in the RM- group (79%) versus the RM+ group (60%), but this was not statistically significant (p=0.1045). Conclusion: This study shows that in a cohort of North American rectal cancer patients, RM+ is associated with male gender and perineural invasion. Patients with positive radial margins show a trend towards decreased OS. Larger studies are needed to investigate factors contributing to positive radial margins after resection for rectal cancer, and to confirm such factors predictive of poor outcome in an attempt to improve surgical decision making.

Associations with positive radial margins after resection

Characteristic	Resection Margin+	Resection Margin-	Total	p-value
Gender				
Male	20	95	115	0.0366
Female	7	65	72	
Distance fram anal verge				0.6163
<5cm	7	44	51	
>5cm	13	101	114	
Type of Surgery				0.8506
Sphincter Preserving Surgery	17	108	125	
Sphincter Sacrificing Surgery	10	52	62	
T-stage				0.02
T0-T2	4	75	79	
T3-T4	16	60	76	
Tx	7	25	32	
N-stage				0.3997
N0	14	88	102	
N1	9	43	52	
N2	3	27	30	
Nx	1	2	3	
Lymph Node Metastasis				0.1992
Present	12	70	82	
Absent	14	88	102	
Perineural Invasion				0.0018
Present	13	18	31	
Absent	13	141	154	
Lymphovascular invasion				0.9664
Present	7	29	36	
Absent	13	117	130	

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Disparities Between Young and Elderly Patients in the First Course of Treatment for Stage II and III Rectal Cancer Y. Tilahun, S. Eubanks, J.P. Arnoletti, S. De la Fuente.* *Surgical Oncology, Florida Hospital Orlando and University of Central Florida, Orlando, FL.*

Background: The use of neoadjuvant chemoradiation for stage II and III rectal cancer is associated with higher rates of resectability, sphincter preser-

vation and improved local control. In elderly patients, however, the feasibility and benefits of this approach are less understood. In this study, we determined disparities in the first course of therapy between young and elderly patients with rectal cancer using the National Cancer Data Base (NCDB). Method: The NCDB was queried for cases of rectal adenocarcinoma diagnosed between 2000-2009. Analyzed variables included patient age, tumor stage, and first course of treatment. For analytical purposes, study groups were divided in young (≤ 69 years of age) or elderly patients (≥ 70 years of age). Results: A total of 8,237 patients that received chemoradiation as initial treatment for rectal cancer were identified from the NCDB during the study period. During the same time, 15,468 patients were treated with surgery first. Fifty-eight percent of patients in the neoadjuvant-first treatment group were younger than 70. Subgroup analysis showed that elderly patients were treated with initial surgery more frequently than with neoadjuvant chemoradiation therapy (surgery-first 72% vs. chemoradiation first 28%, p<0.04). In the contrary, no differences were noted in the first course of treatment received among younger patients (surgery-first 53% vs. chemoradiation first 47%, p=NS). Conclusions: Surgical resection is the favored initial approach for stage II/III rectal cancer patients older than 70 years. Patient age seems to be an important factor that detracts surgeons from adherence to current consensus guidelines in the treatment of stage II/III rectal cancer.

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Immunologic Methods for Defining Malignant Transformation Occurring in Benign Appearing Colonocytes M. Arlen.* *North Shore Univ.Hosp., Manhasset, NY.*

Introduction: Immunohistochemical techniques using specific IgG1's are being used to define malignant transformation occurring in normal appearing colonocytes. We believe that such cells adjacent to tumor are the major cause of anastomotic recurrence. Similarly we have demonstrated that the tumor antigens appearing in transforming colonocytes, shed into the bowel lumen where they can be detected in the stool by a simple ELISA procedure. Information so obtained can be used to determine with a high level of accuracy whether the colon contains a transforming polyp, early carcinoma or is free of pathology. Methods Specific IgG1s have been developed against colon cancer immunogens via use of antigen from pooled human cancer preparations. The monoclonals so defined have been shown to react only with malignant cells expressing antigen. A sandwich ELISA was developed to detect antigen shed into the serum and to define shed antigen from premalignant lesions appearing in stool. Using immunohistochemistry to exam the field affect around colon malignancies we noted that many normal appearing colonocytes expressed the same tumor antigen as did the invading lesion and eventually converted to full malignancy. Results Examination of margins of bowel resection adjacent to tumor showed a high correlation with antigen present in the normally appearing colonocytes and recurrent disease. Detecting these colonocytes at the time of surgery could eliminate the problem of such recurrences. In addition, of the more than 50 stool tests performed, transforming colonocytes as well as various malignancies shedding their tumor antigen into the colon lumen could be identified prior to colonoscopy employing a stool ELISA. Conclusions Specific tumor antigens can be detected in many colonocytes adjacent to a developing malignancy. This determination can be used to prevent anastomotic recurrences. The shedding of antigens from coloncytes as well as tumor into the stool can allow for a stool assay to predict whether a lesion is present or not, and whether colonoscopy is indicated.

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Impact of Aggressive Histology and Location of Primary on the Efficacy of Surgical Therapy for Peritoneal Carcinomatosis of Colorectal Origin J.H. Winer,* J.F. Pingpank, A.H. Zureikat, M.P. Holtzman, L. Ramalingam, H.L. Jones, H.J. Zeh, D.L. Bartlett, S.A. Ahrendt, H.A. Choudry. *Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction Combined cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemoperfusion (HIPEC) for peritoneal carcinomatosis (PC) of colorectal origin increases overall survival (OS) when compared to systemic chemotherapy alone. Signet ring histology demonstrates especially aggressive behavior with poor survival. We sought to determine whether CRS/HIPEC increases survival in this subset of patients. **Methods** We reviewed 67 patients with PC of appendiceal (AP, n=37) or colorectal origin (CRC, n=30) with signet cell histology from a prospective database between May 2001 and August 2011. Multivariate Cox-regression analysis and Kaplan-Meier curves were used to determine prognostic factors for survival. **Results** Median peritoneal cancer index (PCI) for CRC and AP were 12 (IQR 10) and 13 (IQR 8). Complete CRS (CC-0/1) was achieved in 77% and 73% of patients. Six patients (2 CRC, 4 AP) did not receive HIPEC. The average lymph node harvest was 11 (CRC) and 4 (AP) with higher yields for synchronous presentation. 83% of CRC and 92% of AP tumors were high grade. Progression free survival and OS were 7m and 12m in CRC and 12m and 20m in AP patients. In CRC patients, univariate analysis demonstrated that complete CRS improved OS (OS=16m CC-0/1 vs 2m CC2/3; p=0.005), while male gender (OS=13m females vs 6m males, p=0.03) and postoperative grade III/IV morbidity (OS=16m grade I/II vs 6m grade III/IV morbidity, p=0.005) portended poor survival. In AP patients, tumor burden was more important than completeness of cytoreduction (OS=60m PCI< 8 vs 22m PCI 8-16 vs 13m PCI>16 p=0.028) and limited blood loss (OS=20m EBL<1L vs 13m EBL>1L, p=0.05) was essential. In the CRC cohort, multivariate Cox-regression analysis demonstrated complete CRS to be the only independent prognostic factor for survival. **Conclusions** Appendiceal signet cell tumors demonstrate a more favorable outcome than colorectal signet cell tumors after CRC/HIPEC for carcinomatosis, suggesting an underlying difference in biology. Further research and multimodality therapies are essential to improve survival in patients with high-risk histologies.

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Tumor Size as a Prognostic Factor for Colon Cancer Patients Undergoing Sentinel Lymph Node Mapping and Conventional Surgery S. Saha,[1]* M. Shaik,[2] M. Kanaan,[3] B.T. Abadeer,[1] A. Korant,[1] M. Krishnamoorthy,[1] G. Johnston,[1] S. Kaushal,[1] M. Arora,[1] D. Wiese.[1] *1. Surgery, McLaren Regional Medical center, Flint, MI; 2. Hurley Medical Center, Flint, MI; 3. Michigan State University, lansing, MI.*

Introduction: Unlike other solid tumors, tumor size(TS) is not a part of the TNM staging system for colon cancer(CC). Our goal is to study the correlation of TS with TNM staging, nodal positivity(NP), and 5-year overall survival (OS) for patients(pts) with invasive CC undergoing sentinel lymph node mapping (SLNM) vs. conventional surgery (CS). Methods: A retrospective review of 681 pts with invasive adenocarcinoma of the colon were reviewed and divided into two groups of pts(SLNM and CS). The pts in these two groups were subdivided according to the TS in four groups (0-2, 2-4, 4-6 and more than 6 cm). 461 pts underwent SLNM between 1996-2010 compared to 220 pts who underwent CS between 1996-2006. The pathology reports reviewed for TS (the maximum diameter of the primary tumor), T staging, and NP. The OS was calculated from the social security database and our hospital cancer registry. Then all data was compared between both groups. Results: Pts with TS <2cm were mainly T1+T2 (72%, 70%), whereas tumors >6 cm, majority of pts wereT3+T4 (94%, 85%). T1+T2 percentage consistently decreased as TS increased, and T3+T4 percentage was increasing consistently with increased TS (Table 1A). NP according to TS for SLNM pts were (16%, 53%, 56%, 48%) NP and for CS pts were (15%, 32%, 34%, 39%). In both groups, NP increased as TS increased compared to 0-2 cm group. The overall NP in both groups was 47% and 31% (Table 1B). OS for SLNM and CS pts were calculated in each group according to TS. Overall SLNM pts had better OS when compared to CS pts (65 %, 54%). Conclusions: Increasing TS was consistent with increasing T staging for both SLNM and CS pts. NP and OS were worse with increased TS for SLNM and CS pts. SLNM pts had higher NP and better outcome in OS when compared to CS pts, hence TS should be considered as a prognostic factor in pts with adenocarcinoma of the colon.

Table 1A	SLNM		Conventional Surgery	
Size in CM	T1 + T2	T3 + T4	T1 + T2	T3 + T4
0-2	60 (72%)	23 (28%)	24 (70%)	10 (30%)
2-4	54 (31%)	121(69%)	28(38%)	46(62%)
4-6	20(16%)	104(84%)	11(16%)	57(84%)
>6	5(6%)	74(94%)	7(16%)	37(84%)

Table 1B	SLNM		Conventional Surgery	
Size in CM	Nodal Positivity	5 year overall survival	Nodal positivity	5 year overall survival
0-2	16%	81%	15%	71%
2-4	54%	66%	32%	55%
4-6	56%	56%	34%	49%
>6	48%	52%	39%	49%
Total	47%	62%	31%	54%

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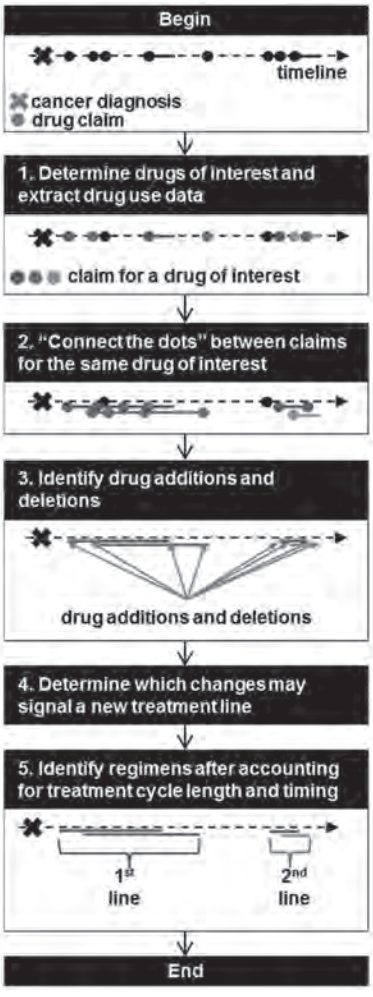
Algorithm for Identifying Various 2nd & 3rd Line Chemotherapy Regimens in Elderly U.S. Medicare Patients With Metastatic Colon Cancer K.A. Bikov,[1] D. Mullins,[1] B. Seal,[2] E. Onukwugha,[1] N. Hanna.[3]* *1. University of Maryland School of Pharmacy, Department of Pharmaceutical Health Services Research, Baltimore, MD; 2. Bayer Healthcare Pharmaceuticals, Inc., Wayne, NJ; 3. University of Maryland School of Medicine, Department of Surgery, Division of General & Oncologic Surgery, Baltimore, MD.*

Background Patients with metastatic colon cancer (mCC) often receive multiple lines of chemotherapy treatment (TX) in response to disease progression or toxicities. A claims-based algorithm that identifies TX lines can provide information on "real world" clinical practice patterns that may not be captured by clinical trials. Methods Our claims-based algorithm was applied to SEER-Medicare data of elderly mCC patients diagnosed in '03-'07 & followed through '09. The algorithm (Figure) included rules for identifying the beginning & end TX lines. The face validity of the algorithm was assessed by: 1) examining the output against a TX map for a random sample of patients; 2) evaluating the overall results; and 3) conducting a sensitivity analysis, which evaluated the variability in the number of detected TX lines as a function of key algorithm parameters. Results Of 7,951 mCC patients, 3,266 (41%) received TX; 1,440 (18% of all, 44% of TX) and 274 (3% of all, 8% of TX) received 2nd & 3rd line TX, respectively. Fewer than 1% of treated patients had a 4th TX line. The utilization patterns in terms of number and type of TX lines were robust to changes in the algorithm parameters. OX±BEV (45%), 5FU/LV±BEV (33%) and IRI±BEV (16%) were the three most common initial TXs. 2nd line TX most commonly consisted of IRI±BIOLOGIC (62%) and OX±BIOLOGIC (26%), but 6% of patients received only BIOLOGICS. CETUX (19%), PANIT (15%), IRI alone (17%) and OX alone (12%) were the most common 3rd line TXs. OX to IRI (49%), IRI to OX (14%), 5FU/LV to OX (12%), and 5FU/LV to IRI (12%) were the most frequent TX progressions for those with 2nd line TX. 5FU/LV to OX to IRI (26%), OX to IRI to BIOLOGICS alone (25%), 5FU/LV to IRI to OX (14%) and IRI to OX to BIOLOGICS alone (6%) were the most frequent TX progressions for those with 3rd line TX. Conclusions Our claims-based algorithm suggests that during '03-'09 relatively few elderly mCC patients received 2nd & 3rd line TX. Sensitivity analysis confirmed the robustness of the algorithm. Future observational studies should address the "real world" benefits and risks of 2nd & 3rd line TX among elderly mCC patients.



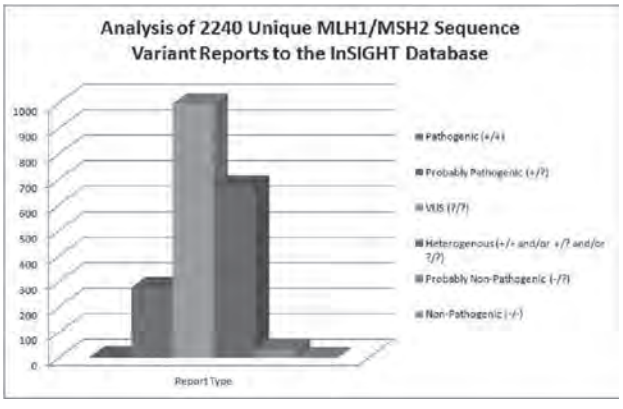
Algorithm Diagram

P144

Expanded Analysis of DNA Sequence Reports on the InSiGHT Database Redefines the Variants of Uncertain Significance (VUS) Clinical Genetics Challenge for Surgical Oncologists R. Raval,[1] T.K. Weber,[1]* L. Baez-Cabrera,[1] A. Abbott,[1] J. Plazzer,[2] F. Macrae,[2] M. Genuardi,[3] S. Okochi.[1] *1. State University of New York Surgical Research Unit at VA New York Harbor Medical Center, Brooklyn, NY; 2. Department of Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, VIC, Australia; 3. University of Florence, Florence, Italy.*

Background: We previously reported to SSO initial analysis of the International Society for Hereditary Gastrointestinal Tumors (InSiGHT) (www.insight-group.org) mismatch repair (MMR) gene database. In 2009 InSiGHT significantly expanded the database. In this study we analyze all MMR gene sequence variants reported to the database. Methods: We analyzed 12,673 DNA MMR gene sequence variants reported on the InSiGHT database (DB) as of July 2012. Our report focused on analysis of unique alterations, and the conclusions of literature cited for the 2,240 unique MSH2 and MLH1 alterations listed. Variants were classified using the following legend: +/+ (pathogenic), +/? (probably pathogenic), ?/? (unknown), -/? (probably non pathogenic), -/- (no known pathogenicity). Variants with conflicting literature reports were noted as "heterogeneous." Results: We noted a dramatic increase in the number of MMR sequence variant reports from 884 in 2008 to 12,673 as of July 2012. For MLH 1, 1150 unique alterations (UAs) were cited of which 168 were classified as "probably pathogenic" having only +/? literature reports. For MSH2, there were 1090 UAs cited of which 108 were classified as "prob-

ably pathogenic". Of the 10,601 MSH2 and MLH1 reports cited only 3 were reported as +/+ indicating the alteration was "pathogenic". Importantly, 50% (996) of MSH2 and MLH1 UAs were listed as "variants of uncertain significance" (?/? reports only). 34% of the combined MLH1 /MSH2 UAs listed were associated with multiple literature reports with differing conclusions for the same variant. Conclusions: InSiGHT DB reports have increased 14 fold since 2009. However literature cited for the 2,240 unique MSH2 and MLH1 alterations reported indicates the clinical significance of 84% of these variants is uncertain. Our results suggest a quantitative analysis/index of the heterogeneous literature cited for most alterations would help prioritize interpretation efforts. These results expand the dimensions of the V.U.S. clinical genetics problem and underscore the importance of continued analysis of the InSiGHT MMR database.



P145

Cytoreductive Surgery with Heated Intraperitoneal Chemotherapy Improves Overall Survival in Patients with Mucinous Signet Ring Peritoneal Malignancies S.J. McPartland,* M.D. Goodman. *Surgery, Tufts Medical Center, Shrewsbury, MA.*

Background: Signet ring pathology is present in a small subtype of mucinous primary peritoneal malignancies, which is a rare neoplasm in itself. Historically, the presence of signet rings is associated with very poor long-term survival. Systemic therapies are usually not effective for primary peritoneal neoplasms; however, cytoreductive surgery with heated intraperitoneal chemotherapy (CRS-HIPEC) has been shown to improve survival. Its application in patients with signet ring pathology has yet to be fully evaluated. Methods: Perioperative and long-term outcomes data were collected on all patients who underwent CRS-HIPEC from 2007 to 2012. The data was then reviewed and those patients with signet ring malignancies or signet ring features were included in the study. Data regarding tumor burden, perioperative outcomes, recurrence-free survival (RFS), and overall survival (OS) were analyzed. Results: Twenty-one patients had signet ring pathology, including two with poorly-differentiated tumors and signet ring features. Average age at time of surgery was 53.1 years. Mean peritoneal cancer index – a measurement of tumor burden with a maximum score of 36 – was 17 (range 3-36). The planned cytoreduction was aborted in 28.6% of patients due to extensive and/or invasive disease. All of the patients who were unresectable at the time of surgery subsequently succumbed to their illness; average OS 161.3 days. Sixty percent of patients who underwent CRS-HIPEC subsequently died; average OS 404.4 days. Of the remaining 40% of patients who underwent CRS-HIPEC, three have had disease recurrence (50%). Conclusions: Mucinous signet ring peritoneal neoplasms, or those with signet ring features, portend a dismal prognosis. Patients with this pathologic subtype have significant tumor burden at time of surgery, which is often unresectable. However, overall survival can be significantly improved in those patients for whom complete cytoreduction and HIPEC are able to be performed. Better pre-operative measures for determining resectability need to be developed.

P146

Panobinostat, a Novel Histone Deacetylase Inhibitor, in Metastatic Medullary Thyroid Cancer and Iodine-refractory Differentiated Thyroid Cancer S.E. Murray,[1]* A.M. Traynor,[2] G.E. Leverson,[1] D.F. Elson,[3] H.R. Hernan,[2] M.M. Larson,[2] J.H. Blank,[4] H. Chen,[1] R.S. Sippel.[1] *1. University of Wisconsin School of Medicine and Public Health, Department of Surgery, Section of Endocrine Surgery, Madison, WI; 2. University of Wisconsin Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Division of Hematology/Oncology, Madison, WI; 3. University of Wisconsin School of Medicine and Public Health, Department of Medicine, Division of Endocrinology, Madison, WI; 4. Green Bay Oncology, Green Bay, WI.*

Introduction: Histone deacetylase (HDAC) inhibitors suppress tumor cell proliferation in medullary thyroid cancer (MTC) and differentiated thyroid cancer (DTC) in vivo. We present early results from our multicenter phase II trial of panobinostat, a potent inhibitor of Class I, II, and IV HDAC enzymes, in MTC and radioactive iodine (RAI)-refractory DTC. Methods: We have enrolled 10 patients (pts) to date with progressive metastatic MTC or RAI-refractory DTC. Panobinostat was given at 20 mg orally TIW until disease progression or intolerable toxicities. The primary objective was anti-tumor response rate; secondary objectives included overall survival (OS), progression-free survival (PFS), tolerability, and changes in serum thyroglobulin (Tg) concentration. Results: Mean age was 58±13 yrs; 7 pts were female. 9 pts had DTC, and 1 pt had MTC. Median study follow-up was 11.1 months (mos). Median duration of treatment was 2.3 mos (range, 0.8-7.2). Stable disease (SD) was seen in 5 pts, with a median duration of 5.8 mos (range, 3.6-13.8). All 5 SD pts are currently alive, including 1 with SD 7.2 mo on treatment. Progressive disease (PD) was seen, and was the cause of death, in 5 pts. No anti-tumor responses have been observed. Median PFS for the 10 pts was 2.4 mos (95% CI, 0.9-5.8), with 2 pts having a PFS longer than 6 mos. Median OS for the 10 pts was 18.4 mos (95% CI, 1.5-not estimable). 4 of 9 pts had reductions of their serum Tg on study; however, changes in serial Tg values did not distinguish PD from SD pts. 7 pts required 1 or more dose holds/reductions due to thrombocytopenia (n=5), neutropenia (n=1), diarrhea, (n=1), or asthenia (n=1). 3 pts were withdrawn from therapy due to thrombocytopenia or neutropenia. Of the 3 pts with ≥ grade 3 thrombocytopenia, 2 had no bleeding. The third pt continued to bleed from her chronically erosive tumor, without exacerbation. Febrile neutropenia and QTc prolongation were not observed. Conclusions: Panobinostat yielded SD in half of our actively progressing pts. This promising disease stabilization warrants further evaluation. Accrual to our protocol continues to a total of 33 pts.

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Pancreatic Neuroendocrine Tumors in Von Hippel Lindau Syndrome: An Assessment of Tumor Growth and Radiographic Density A. Weisbrod,[2]* M. Kitano,[3] F. Thomas,[1] D. Williams,[1] N. Gulati,[1] K. Gesuwan,[1] Y. Liu,[1] D. Venzon,[1] A. Venkatesan,[1] J. Yao,[1] S.K. Libutti,[3] N. Nilubol,[1] E. Kebebew.[1] *1. National Institutes of Health, Bethesda, MD; 2. Walter Reed National Military Medical Center, Besthesda, MD; 3. Montefiore Medical Center, Bronx, NY.*

Background: Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of rare tumors. Only a subset will progress to malignant disease which is associated with a poor prognosis. There is limited data on the natural history of these tumors and it is difficult to determine which tumors require intervention because of the risk of malignancy. Methods: A prospective study of 134 patients with Von Hippel Lindau syndrome with solid pancreatic lesions was conducted to determine the natural history of these tumors with comprehensive biochemical testing, axial and functional imaging and advanced imaging analysis. Results: Solid enhancing lesions consistent with PNETs demonstrate a non-linear growth pattern, with both inter- and intra-tumor variation. Approximately 20% of lesions decrease in size and 20% showed no growth. This included 2 of 4 surgically-proven malignant tumors which had a net decrease in primary tumor size over time. Tumor volume, as derived from greatest diameter and volumetric measurement, showed correlation to actual measured volume in surgically resected tumors (Spearman rank correlation ρ=0.72, p=0.0011, and ρ=0.83, p<0.000; respectively). Tumor density measurement had an inverse relationship with tumor size (Spearman rank correlation -0.22, p=0.0047) and a tumor density of 200 was 75% specific for metastatic disease. Serum Chromogranin A (CgA) levels showed an inverse trend to tumor size

(p=0.053, n=137); however there was no relation to serum pancreatic polypeptide levels. There was a positive association between tumor size and 18F-FDG-PET Scan SUV (p=0.0059). Conclusions: PNETs demonstrate a non-linear and variable growth pattern which includes decrease in tumor size. Tumor density may be useful for predicting which lesions have a high risk of malignancy.

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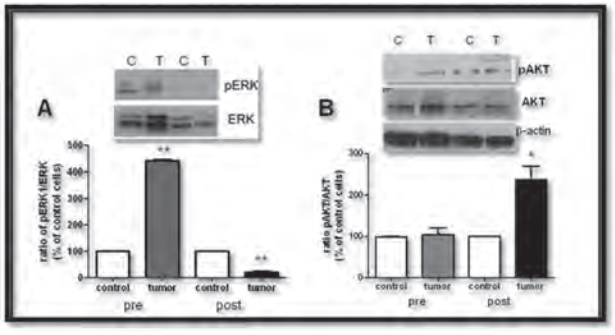
An Evaluation of Surgeon-performed Neck Ultrasound and Sestamibi Scans for Preoperative Tumor Localization in Secondary and Tertiary Hyperparathyroidism Y. Tasci, H.E. Taskin, S. Aliyev, O. Agcaoglu, E. Aksoy, J. Mitchell, M. Milas, J. Shin, A. Siperstein, E. Berber.* *Endocrine Surgery, Cleveland Clinic, Cleveland, OH.*

Background: The role of localization studies in secondary (SHP) and tertiary (THP) hyperparathyroidism has not been well defined. Our aim is to analyze the utility of surgeon-performed neck ultrasound (US) and sestamibi scans (MIBI) in these patients. Methods: The records of patients who underwent parathyroidectomy for SHP (n=67) and THP (n=35) within 10 years were reviewed from an IRB-approved prospective database. An analysis of whether localizing studies affected the conduct of a 4-gland exploration was done. Results: Subtotal parathyroidectomy with bilateral cervical thymectomy (BCT) was performed in 94% and total parathyroidectomy with autotransplantation in 6%. All 4, 3, 2, 1 and 0 glands were seen by US in 43%, 16%, 22%, 10% and 7% of patients, and by MIBI in 8%, 3%, 33%, 27% and 10%, respectively. MIBI was overall superior to US in 6%. Unknown thyroid pathologies were detected in 21% with US. 35 patients had ectopic glands, seen by US in 13 (37%) and by MIBI in 12 (34%). Excluding thymic glands removed by routine BCT, the benefit of US and MIBI, to change the conduct of a 4-gland exploration, was 7% and 6%, respectively. Conclusions: Our study shows that, only in 6-7% of the time, localizing studies provide information to change the conduct of a 4-gland exploration in SHP and THP. Due to its detection of unsuspected thyroid pathology in 21%, we believe that there is a role for preoperative US in these patients. However, these results question the routine use of MIBI scans in these patients.

P149

Estrogen Receptor Expression Promotes Papillary Thyroid Cancer Progression in Women B.J. Allan,* P. Catanuto, S.J. Elliot, J.I. Lew. *Surgery, University of MIami, Miami, FL.*

Introduction: Estrogen and its receptors may play an important role in the development of papillary thyroid cancer (PTC). Furthermore, PTC may present more aggressively in post-menopausal women with higher rates of metastasis and recurrence compared to pre-menopausal women. This study examines the differences in estrogen receptor subtype alpha (ERα) expression and intracellular ERK and PI3K/Akt pathway activation in pre- and post-menopausal women with PTC. Methods: Pre-menopausal women (n=3; 21-40 yrs. with regular menstrual cycles) and post-menopausal women (n=3; >55 yrs. with last menstrual period 1-yr prior to enrollment) were stratified into 2 groups. Human PTC cells from index tumor and normal (control) thyroid cells from contralateral thyroid lobe were derived from fresh surgical specimens. PTC was confirmed by final histopathology. ERα, ERK and PI3K/Akt expression were determined by Western blot analysis. Matrix metalloproteinase (MMP-2) activity, a marker of invasion, was measured by zymography. Quantified by densitometry, values are expressed as percent of controls. Results: PTC cells from post-menopausal women had 2.5 fold higher ERα expression compared to their control tissue ($p<0.005$) whereas PTC cells from pre-menopausal women had an averaged decrease of ERα expression by 23% compared to controls ($p=0.05$). PTC cells from pre-menopausal women had a 4 fold increase in ERK ($p<0.005$) and no change in Akt activation compared to their controls, respectively. Conversely, PTC cells from post-menopausal women had an insignificant decrease in ERK activation, and 2.5 fold increase in Akt activation ($p<0.05$). Lastly, MMP-2 activity was 4 fold higher in post-menopausal women compared to controls ($p<0.005$), whereas this activity was not statistically higher in pre-menopausal women. Conclusions: Although ERK represses ERα expression in pre-menopausal women, increased Akt activation and MMP-2 activity is associated with increased ERα expression in post-menopausal women with PTC. Such alterations in hormone receptor expression and intracellular signaling may determine, in part, more aggressive PTC behavior in post-menopausal compared to pre-menopausal women.



P150

Radioiodine Utilization in Adolescent and Young Adult (AYA) vs. Non-AYA Thyroid Cancer Patients M. Goldfarb,* S.S. Sener. *Sur-gery, University of Southern California Keck SOM, Los Angeles, CA.*

Background: Differentiated thyroid cancer (DTC) is one of the top five cancers among adolescents and young adults (AYA: aged 15-39 years). Though the majority of patients in this age group are considered low risk compared to older patients, there are no specific treatment recommendations. The potential adverse effects of radioiodine (RAI) therapy for this age group include second malignancies and difficulties with fertility. This study compares the factors influencing RAI utilization in AYA and non-AYA patients. Methods: 5687 primary DTC patients were identified from the SEER database between 1/1/04 - 1/31/09. The 2009 American Thyroid Association (ATA) guidelines were used to classify patients as low (LR) or intermediate/high risk (IHR) based on tumor characteristics. Multivariate logistic regression analysis was performed. Results: 56.9% of AYA (n=1963) patients received postoperative RAI compared to 52.2% of non-AYA (n=3724) patients (p=.001). For AYA patients, having a total thyroidectomy (TT) (OR 3.53 CI: 2.7-4.61, p<.001) predicted RAI in a multivariate model, whereas LR status (OR 0.52 CI: 0.43-0.63, p<.001) and northeast residence (NE) (OR 0.39 CI: 0.29-.52, p<.001) decreased the probability of RAI. All three factors similarly affected non-AYA patients (TT: OR 3.18 CI: 2.65-3.82, p<.001; LR: OR 0.44 CI: 0.38-0.51, p<.001; NE: OR 0.36 CI: 0.27-0.49, p<.001) in addition to an increased likelihood after a lymph node dissection (OR 1.72 CI: 1.44-2.05, p<.001). In a subset having TT (n=1077), no factor influenced RAI use in AYA patients, whereas LR (OR .30 CI: .21-.43, p<.001) and NE (OR 0.39 CI: 0.19-0.79, p=.008) were associated with decreased use in non-AYA patients. Conclusion: Despite their young age, AYA patients are more likely to receive postoperative RAI for thyroid cancer compared to non-AYA patients. Extent of thyroidectomy, ATA risk classification, and geographic location play a role in RAI utilization across all age groups. Whether statistical significance equates with clinical significance in this analysis is debatable. Increased awareness of the unique survivorship implications for AYA patients will be an important aspect to address going forward.

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A Single Parathyroid Hormone Level Obtained 4 Hours after Total Thyroidectomy Predicts the Need for Postoperative Calcium Supplementation A.A. Carr,* T.W. Yen, A.K. Cayo, S.M. Misustin, K. Wall, D. Evans, T.S. Wang. *Surgical Oncology, Medical College of Wisconsin, Milwaukee, WI.*

Introduction Postoperative parathyroid hormone (PTH) levels after total thyroidectomy have been shown to predict the need for routine calcium supplementation. The aim of this study was to determine whether a single PTH level drawn 4 hours (4hr) postoperatively or the morning of postoperative day 1 (POD1) most accurately identifies patients who do not need routine supplementation. Methods This study is a single institution retrospective review of patients who underwent total thyroidectomy from January 2012 to September 2012 and had 4hr and POD1 PTH levels. If PTH ≥10, patients received no routine supplementation unless they reported hypocalcemic symptoms; if PTH <10, patients received oral calcium carbonate ± calcitriol. Results Of the 77 patients, 20 (26%) had 4hr PTH <10 and 18 (23%) had POD1 PTH<10 (Table). No patient with a 4hr PTH >10 had a POD1 PTH <10; two had 4hr PTH <10 (7.5 and 8.3) but POD1 PTH ≥10 (10.2 and 13.4, respectively). Of 13 (17%) patients who reported hypocalcemic symptoms, nine had 4hr and POD1 PTH

<10 and received routine supplementation. Of the remaining four patients, two received routine calcium supplementation due to persistent symptoms (one had 4hr PTH <10 but POD1 PTH ≥10 and one had both 4hr and POD1 PTH ≥10); two had transient, self-limited symptoms (4hr and POD1 PTH ≥10). The table summarizes the diagnostic ability of 4hr and POD1 PTH in predicting the need for routine calcium supplementation. A 4hr PTH level has higher sensitivity and equivalent specificity and negative predictive value than a POD1 PTH level. Median duration of postoperative supplementation was 17 days (range 1-179). Conclusion Use of a single 4hr PTH level as a guide for routine postoperative calcium supplementation assures that at-risk patients are detected and supplemented in the immediate postoperative period while minimizing the number of patients who may receive unnecessary calcium supplementation. Patients who undergo same-day thyroidectomy and have a PTH ≥10 at 4 hours postoperatively may be safely discharged home without routine calcium supplementation.

	Number of patients (%)						
	PTH <10	PTH ≥10	Median PTH value (pg/mL; range)	SN	SP	PPV	NPV
4 hour PTH	20 (26)	57 (74)	21.1 (2.3-97.1)	95	98	95	98
POD1 PTH	18 (23)	59 (77)	23.2 (2.4-61.3)	90	100	100	97

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; SN, sensitivity; SP, specificity

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Prognostic Factors and Survival in Anaplastic Thyroid Cancer: A Population-based Study in North-East Netherlands J.T. Plukker,[1]* L. Steggink,[1] B. Van Dijk.[2] *1. Dept Surgical Oncology, University Medical Center Groningen, Groningen, Groningen, Netherlands; 2. National Cancer Center Netherland, Utrecht, Utrecht, Netherlands.*

Introduction: Anaplastic thyroid carcinoma (ATC),is one of the most aggressive tumors. We investigated whether pre-existent goiter was associated with survival and analyzed clinically relevant characteristics to identify prognostic factors related to survival.Patients and Methods: Population-based study of all ATC patients from the Netherlands Cancer Registry diagnosed in 20 hospitals in North-East Netherlands between 1989 and 2009. All available data from medical records were collected.To assess prognostic risk factors with respect to survival a multivariate Cox regression analysis was used in correlation with patient characteristics and therapy.Results: In 94 of the 108 patients additional data was obtained from medical records. Median age was 74 (IR 67 – 80) years and 81% were women (N=76). Patients presented with hoarseness (N=39; 41.5%) and/or stridor (N=23; 24.5%). ATC was diagnosed by fine-needle aspiration in 64.9% (n=61) and by either tru-cut needle biopsy in 35.1% (n=33) or open biopsy in 14.9% (n=14). Twenty-nine patients (30.9%) had pre-existent goiter, of which 8 (8.5%) with WDTC. At time of diagnosis, the median tumor size was 7.0 (IR 5.0 – 8.0) cm, 44 (46.8%) patients had nodal involvement and 41 (43.6%) had distant disease, usually in the lung (n=35); combined with bone (n=3) or cerebral metastases (n=1). Total or partial/hemithyroidectomy were performed in 13 and 9 patients, respectively. Radiotherapy was used in 51 patients with a median total dose of 39 Gy (IR 27.8-64) with a median of 15.5 fractions (IR 8.8 – 33). The 1-year OS was poor: 9% (95% confidence interval; CI 3% – 14%) with no difference in survival (p=0.42) or in 1-year OS between pre-existent goiter (14%; 95% CI: 1-26%) and without goiter (6%; 95% CI: 0-13%). The hazard to die was lower for patients treated with surgery (HR 0.39, 95% CI 0.22 – 0.69, p=0.001) and/or radiotherapy (HR 0.22, 95% CI 0.12 – 0.41, p<0.001). Conclusion:Survival in ATC patients was poor, and not different for patients with pre-existent goiter. Radiotherapy and/or surgery, when possible, have a positive effect on survival.

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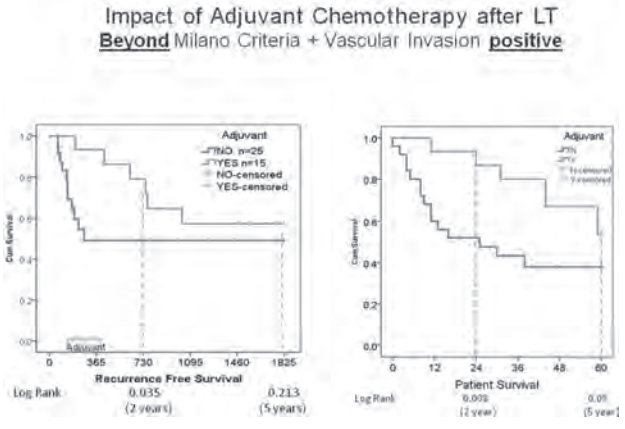
Adjuvant Chemotherapy after Liver Transplantation for Hepatocellular Carcinoma (HCC) with Lymphovascular Invasion (LVI) Reduces the Risk of Early Recurrence K. Uchida,* D.M. Levi, L. Feun, T. Dohi, T. Hibi, L. Mosna, J. Fan, A. Tekin, G. Selvaggi, E. Maki, D. Weppler, M.T. Garcia, S. Nishida, T.G. Andreas. *University of Miami, Miami, FL.*

Introduction: Since adoption of MELD prioritization for curative liver transplantation to HCC preoperatively within Milan Criteria, the risk associated with HCC recurrence under this allocation system was investigated. The benefit for adjuvant chemotherapy following for high risk of HCC recurrent has been suggested, however its value has not been well studied. Patients and methods: The records of all 275 consecutive patients with HCC fulfilled the Milan criteria preoperatively and underwent deceased donor liver transplant between Mar 2002–Dec 2010 at our center were reviewed. Eighty patients who had LVI positive in explants pathology were recommended adjuvant chemotherapy of either Doxorubicine or Sorafenib. Risk factor associated with recurrence, recurrence and survival rate were analyzed and assess the benefit of adjuvant therapy by comparing the groups with and without adjuvant therapy. Result: Thirty-four patient accepted adjuvant therapy, and actually 28 (82.3%) could started adjuvant chemotherapy, and 15 (44.1%) completed the adjuvant treatment at least 5 months. Median time to start the treatment was 95 days after transplant. Seventeen patients (50.0%) could not start or had to discontinue the treatment within 5 months due to early recurrence of HCC (n=7), HCV recurrence (n=6), congestive heart failure (n=3), biliary complication, financial problem and poor general condition (n=1). In the population of HCC with both over Milan criteria and LVI positive, 2- year recurrent free survival were 49.1% in control group and 79.0% in adjuvant group. (Log-Rank p=0.035). Two-year and 5 year patient survival were both significantly higher in adjuvant (93.3% and 53.3% respectively) than control (52.0% and 37.9% respectively) (p=0.008 at 2 years and p=0.05 at 5 years). In the population of HCC both within Milan criteria and LVI positive, no patients had recurrence HCC in adjuvant group (n=5), however 7 patients (20.0%) had reoccurrence in control group within 5 years. Conclusion: Adjuvant chemotherapy after liver transplantation for HCC with LVI reduces the risk of early recurrence.



P154

Understanding Variations in Referral Patterns and Treatment Choices for Patients with Hepatocellular Carcinoma O. Hyder, D. Cosgrove, H. Nathan, K. Hirose, C. Wolfgang, J. Bridges, J. Geschwind, N. Bhagat, A. Gurakar, J.M. Herman, I. Kamel, T. Pawlik.* *Surgery, Johns Hopkins University, Baltimore, MD.*

Background: Patterns of care of physician specialists may differ for patients with hepatocellular carcinoma(HCC). The extent and reasons underlying possible variations are poorly understood. One source of variation may be disparate referral rates to specialists leading to differences in cancer-directed treatments. Methods: We queried the Surveillance, Epidemiology, and End Results(SEER) linked Medicare database for patients with HCC diagnosed between 1998-2007 who consulted one or more physicians following diagnosis. Visit and procedure records were abstracted from Medicare billing records and factors associated with visiting a specialist and subsequent treatment were examined. Results: 6752 patients with HCC were identified;median age was 73 yrs and the majority was male(66%), White(60%) and from a West geographical region(56%). 1379(20%) patients had early-stage disease. In the six months after diagnosis, referral to a specialist varied considerably (hepatology/gastroenterology-60%; medical oncology-62%; surgery-56%; interventional radiology-33%; radiation oncology-9%). 22% patients saw one specialist, while 39% saw ≥3 specialists. Time between diagnosis and visitation with a specialist varied by sub-specialty (surgery-37 days vs. interventional radiology-55 days;P=0.04). Factors associated with referral to a specialist included younger age(OR=2.13), geographic location(Northeast OR=2.09), and presence of early-stage disease(OR=2.21)(all P<0.05). Among patients with early-stage disease, 77% saw a surgeon, while 50% had a medical oncology consultation. Receipt of therapy among patients with early-stage disease

varied (no therapy-30%; surgery-39%; interventional radiology-9%; other-22%). Factors associated with receipt of therapy included younger age(OR=2.82), as well as time to consultation with cancer specialist(OR=1.05)(both P<0.05). Conclusions: Following HCC diagnosis, referral to a specialist varied considerably. Both clinical and non-clinical factors were associated with consultation. Variations in referral to a specialist and subsequent therapy need to be better understood to ensure all HCC patients receive appropriate care.

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Ablation for Hepatocellular Carcinoma: Validating the 3cm Breakpoint R.T. Groeschl,* T. Gamblin, K.K. Turaga. *Medical College of Wisconsin, Milwaukee, WI.*

INTRODUCTION: Although many previous studies on ablation outcomes for hepatocellular carcinoma (HCC) have dichotomized tumor size around a 3cm cutoff to determine prognostic significance, a growing number of reports describe excellent outcomes for larger tumors. To address the sensibility of this somewhat arbitrary 3cm cutoff, we stratified patients by 1cm tumor size intervals and hypothesized that disease-specific survival (DSS) would not vary significantly between adjacent groups. METHODS: Patients treated with local ablation for T1 HCC (≤8cm) were identified from the Surveillance, Epidemiology, and End Results database (2004-2008). Log-rank tests were used to compare DSS curves of adjacent study groups, and multivariable Cox proportional hazards models were used to adjust for age, gender, alpha-fetoprotein level, and cirrhosis when comparing the DSS of adjacent study groups. RESULTS: There were 1,093 patients included in the study (26% female, median age: 62 years). The 3-year DSS was significantly lower in patients with 3-4cm tumors compared to 2-3cm tumors (58% vs 72%, p=0.002, Table 1). In adjusted models, DSS did not vary significantly between any size intervals up to 3cm. Patients with 3-4cm tumors, however, had a poorer prognosis compared to patients with 2-3cm tumors (hazard ratio: 1.60, 95% confidence interval: 1.18-2.18, p=0.002). DSS also fell significantly when tumor size increased from 5-6cm to 6-7cm (53% vs 21%, 0.006). Age and alpha-fetoprotein levels were also independently predictive of DSS in most multivariable models; however, the presence or absence of cirrhosis was not predictive in any models (smallest p=0.382). CONCLUSIONS: This study defends the use of a 3cm breakpoint when studying outcomes after ablation for HCC. Although some have advocated that ablation is more successful in cirrhotics, we found no evidence for this in our study.

DSS in Patients with Solitary HCC Undergoing Local Ablation, Stratified by Tumor Size

Size Group	n	3-year DSS (%)	p*
≤1cm	12	65	-
1-2cm	213	69	0.816
2-3cm	310	72	0.278
3-4cm	245	58	0.002
4-5cm	145	52	0.148
5-6cm	89	53	0.809
6-7cm	37	21	0.006
7-8cm	32	27	0.343

DSS = disease-specific survival, HCC = hepatocellular carcinoma
*a separate log-rank test compares each DSS curve to the previous size group; for example, the p-value of 0.278 shown for the 2-3cm group represents a comparison of the 1-2cm group (69% 3-year DSS) vs the 2-3cm group (72% 3-year DSS)

P156

Robotic-assisted Right Hepatic Resection M. Sabbaghian,* D.L. Bartlett, A. Tsung. *Surgery, Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA.*

PURPOSE: Robotic-assistance offers several advantages for certain surgical procedures. Its use has been and is being investigated for its application in liver resection. This video demonstrates robotic-assistance for right hepatic resection with laparoscopic technique used to isolate and ligate the right hepatic vein in an extra-hepatic manner. Method: The Da Vinci Surgical System was used in combination with laparoscopy to isolate and resect the right hepatic lobe in a patient with colorectal cancer metastatic to the liver. Results/Conclusion: Robotic-assisted right hepatic resection can be safely achieved. Laparoscopy is helpful for extraparenchymal isolation/ligation of the right hepatic vein when this is important.

P157

Surgical Placement of Biological Mesh Spacers to Displace Bowel from Unresectable Liver Tumors Facilitates Safe Delivery of Dose-intense Radiation Therapy A.B. Haynes,[1]* T.A. Aloia,[1] J. Vauthey,[1] C. Ferrone,[2] C. Crane,[1] J.Y. Wo,[2] T.S. Hong,[2] S.S. Yoon.[2] *1. Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; 2. Massachusetts General Hospital, Boston, MA.*

Introduction: Delivery of radiation therapy (RT) to unresectable liver tumors is frequently limited by proximity of radio-sensitive organs. Methods: On IRB approved protocols, biological mesh spacers (BMS) composed of acellular human dermis were placed via laparoscopic or open approach to displace bowel from unresectable liver tumors in patients (pts) who were previously unable to receive RT due to risk of bowel toxicity. RT was delivered via proton beam (PBRT), intensity modulated (IMRT), or stereotactic body (SBRT) techniques. Results: In one year, 14 pts were treated. Median pt age was 64 yrs (46-83). Diagnoses included intrahepatic cholangiocarcinoma (IHC) (n=6), hepatocellular carcinoma (n=3), and metastases (n=5). A solitary lesion was present in 8 pts, while 4 pts had 2 lesions and 2 pts had 3 lesions. Median largest tumor size was 6.3 cm (1.6-17.5 cm). Extrahepatic disease was present in 5 pts (lymph nodes 3, bone 2, and primary tumor 1). The surgical approach was laparoscopic in 9 pts and open in 5 pts. Organs mobilized for spacer placement included stomach (n=11), duodenum (n=7), and colon (n=6). Folded, extra thick (2.3-3.3 mm) BMS were used, with a median area of 384 cm^2 (256-640 cm^2). Median operating time was 118 min (57-232 min). Median length of stay was 2.5 days (1-8); 3 pts developed low-grade complications (abdominal wall hematoma, cellulitis, ileus). Postoperative imaging confirmed eligibility to receive RT with >1cm buffer to sensitive structures. Two pts did not receive RT due to extrahepatic disease progression. For the remaining 12, RT was delivered by PBRT in 8 pts, IMRT in 3 pts, and SBRT in 1 pt. Median total dose delivered was 54 Gy (40-58.5) in 5-15 fractions, with no reports of grade 3-4 bowel toxicity. At last follow-up, local disease control was obtained in 11 of 12; 4 of 6 IHC pts were also without evidence of extrahepatic disease after 4-14 months. None of the BMS required removal. Conclusions: Initial dual institution experience with this novel technique demonstrates safety and efficacy, allowing previously untreatable liver tumor patients to receive high-dose RT.

P158

Patients with Cirrhosis and any Indeterminate Nodule by Surveillance Imaging Have a High Risk of Developing HCC S.P. Albert,[1]* M. McNally,[2] L.A. Shirley,[1] R. Sullivan,[1] S. Abdel-Misih,[1] M. Bloomston,[1] C. Schmidt.[1] *1. Surgical Oncology, Ohio State Medical University, Columbus, OH; 2. Saint Luke's Health System of Kansas City and University of Missouri-Kansas City, Kansas City, KS.*

Introduction: There are defined criteria for the imaging diagnosis of hepatocellular carcinoma (HCC) in the cirrhotic patient. However, the risk for the development of HCC in those patients felt to have an indeterminate nodule by imaging is unknown. In patients with cirrhosis, the risk of developing HCC ranges from 5-30% over 5 years, and surveillance imaging with AFP levels are recommended every 6-12 months. Indeterminate nodules in this setting are sometimes a diagnostic dilemma. We examined the incidence of HCC in our patients with cirrhosis and any indeterminate nodule on surveillance imaging. Methods: We identified 252 patients with cirrhosis, no prior history of HCC, at least one indeterminate nodule seen on multi-phase contrast- enhanced CT/MRI and reviewed as part of a high volume multi-disciplinary liver tumor board. Patients with an indeterminate nodule were then followed every 3 months with imaging until diagnosis of HCC or resolution of the nodule. The incidence of HCC development in indeterminate nodules was calculated and risk factors for development of HCC were determined by multivariate logistic regression analysis. Results: The median follow-up after the diagnosis of indeterminate nodule was 15.3 months. The incidence of HCC in this population was 21% (53 of 252), and the median time to development of HCC was 2.7 months (range 0-25.9 months). The independent risk factors associated with increased risk for HCC were low platelets, increased age, viral hepatitis, and male gender (Table). Conclusions: The incidence of HCC in patients with cirrhosis and an indeterminate nodule may be as high as one in five. Patients with cirrhosis, viral hepatitis and any indeterminate nodule are an ideal population for studies examining chemoprevention of HCC or identification of novel biomarkers to increase early detection.

Factor	RR (95% CI)	Univariate	Multivariate
Male Gender	2.60 (1.29-5.24)	<0.01	0.02
Any viral hepatitis	2.38 (1.26-4.49)	<0.01	0.01
Age at DX nodule	1.03 (.995-1.06)	0.09	0.01
AFP at DX nodule	1.00 (.998-1.01)	0.58	—
Platelets	0.988 (.981-.995)	<0.01	0.01
Total bilirubin	1.01 (.924-1.11)	0.77	—
INR	0.836 (0.466-1.50)	0.55	—
Albumin	0.851 (0.658-1.100)	0.22	—

P159

Improved Anti-Metastasis Efficacy of Non Anticoagulant Heparin Derivative versus Low Molecular Weight Heparin (LMWH) in Mouse Pancreatic Tumor Models R. Alyahya,[1]* S. Thangirala,[3] A. Nigam,[2] S. Stain,[2] S. Mousa.[3] *1. albany college of pharmacy and health science, albany, NY; 2. albany medical center, albany, NY; 3. Pharmaceutical Research Institute, albany, NY.*

Introduction: Heparin and its derivatives are known to attenuate cancer metastasis, but have not been used clinically due to adverse bleeding effect. This study examined the ability of a non-anticoagulant LMWH (NACH) to inhibit metastasis of a growing primary mass and metastasis following surgical excision of primary tumor in pancreatic mouse model. Methods: Two experiments were conducted using athymic female mice. In the first experiment, 3 groups of mice (n = 8 per group) received 10 mg/kg subcutaneous injections of saline, LMWH or NACH and thirty minutes later, luciferase transfected pancreatic cancer cells (Mpanc96) at 1 x 106 cells were implanted into the mouse spleen and the treatment continued daily for a month. Xenogen IVIS imaging was obtained once a week to measure metastatic load to various organs. The tumor burden measurements were based on the bioluminescence signal intensity of the pancreatic cancer cells. In the second experiment, Mpanc96 cells 0.5 x 106 were injected into the tail of the pancreas and one week later animals received NACH, LMWH, or saline 30 minutes before resection of the pancreatic tumor followed by daily treatment for 3 weeks. Tumor metastasis was evaluated by IVIS imagining. Bleeding time was determined by cutting 0.5 cm from the tip of the tail, immersing the tail in water, and recording the time until the tail stopped bleeding. Results: NACH significantly decreased the level of metastasis in our experimental metastasis (P< 0.05) and surgically induced metastasis (P= 0.017) versus control and LMWH. NACH did not significant affect bleeding time as compared to control or LMWH, while LMWH significantly (P = 0.022) prolonged bleeding. Conclusion: These data suggest that NACH is an effective and safe anti-metastatic agent and warrant further clinical evaluation.

P160

Outcomes for Resection of Recurrent Intrahepatic Cholangiocarcinoma P. Tabrizian,* G. Jibara, J.F. Hechtman, B. Franssen, D. Labow, S.N. Thung, M.E. Schwartz, U. Sarpel. *1Mount Sinai School Of Medicine, New york, NY.*

Introduction: While surgical resection is the treatment of choice for primary intrahepatic cholangiocarcinoma (IHC), the optimal approach to recurrent cholangiocarcinoma remains unclear. Specifically, the role of resection for isolated metastases or intrahepatic recurrences is not well established. The aim of this analysis was to examine the prognostic features and outcomes of patients undergoing treatment for recurrent IHC. Methods: A retrospective chart review was performed on all patients undergoing resection for primary IHC 1995-2009. Clinical data were abstracted and statistical analyses were conducted in the standard fashion. Results: 70 patients underwent hepatectomy for primary IHC. Median survival from time of primary resection was 29±6 months. Recurrence developed in 40 (57%) patients at a median of 18±4 months. These recurrences were treated with surgical resection in 12 (30%), locoregional therapy in 12 (30%), systemic therapy alone in 9 (23%), and supportive care in 3 (8%) patients. Median survival from time of recurrence was 19±2 months. Predictors of survival after recurrence are summarized in Table 1. The one and three-year survival rates after treatment of recurrence were 91 % and 55 % for repeat resection, 83 % and 29 % for locoregional therapy, and 75 % and 0 % for those who received systemic chemotherapy, respectively. Conclusion: Recurrence can be expected to occur in over half of patients undergoing curative resection for IHC. Patients with recurrent IHC after resection represent a diverse group with a wide range of outcomes. Meaningful survival can be achieved with repeat resection in carefully selected patients.

Table 1: Predictors of survival after recurrence (n=40)

Variable	n (%)	p value
Age Mean (SD)	61.8 (11.8)	NS
Male gender	17(42.5)	NS
Solitary tumor	20 (50.0)	p<0.05
Site of recurrence Intrahepatic Extrahepatic Intra-extrahepatic	28 (70.0) 9 (22.5) 3 (7.5)	NS
Time of recurrence (months) ≤12 12-24 > 24	22 (55.0) 13 (32.5) 5 (12.5)	NS
Treatment of recurrence Repeat resection Locoregional therapy Embolization RFA XRT Systemic chemotherapy alone No treatment	12 (30.0) 12 (30.0) 8 (20.0) 2 (5.0) 2 (5.0) 9 (22.5) 3 (7.5)	p<0.001

P161

Outcomes after Emergency Surgery in Naïve GIST Patients F. Gerstenhaber,[1]* A. Kapiev,[3] S. Grunner,[2] G. Bar- Sela,[2] E. Itzkowitz,[1] O. Merimsky,[1] Y. Kluger,[2] A. Halevy,[3] J.M. Klausner,[1] G. Lahat.[1] *1. Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; 2. Rambam, Haifa, Israel; 3. Assaf Harofeh, Tzrifin, Israel.*

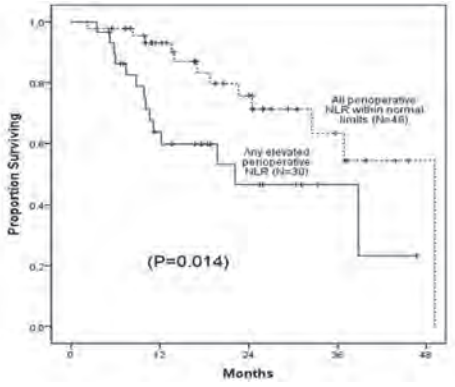
Background: Our aim was to evaluate clinicopathologic characteristics of naïve GIST patients who had emergency surgery and to determine their management and outcomes. Methods: The medical records of 310 GIST patients treated between 1994- 2012 in three referral centers were reviewed. Clinical, pathological, treatment, and outcome characteristics of naive patients who had emergency surgery within 72h from their admission to the ER were analyzed. These were compared to a matched cohort of GIST patients treated electively over the same time period. Median follow-up length was 49 months; imatinib was administered to patients operated on between 2004- 2012 upon the decision of a multidisciplinary team. Mutation analysis to be performed. Results: Thirty- eight patients were identified and included in our study cohort; their median age was 65 years (range, 32-96), 54% were men (n=20). Thirty-three patients (85%) had localized tumors, whereas five (15%) were metastatic at initial presentation. Eighteen patients (47%) required emergency surgery due to tumor rupture, 13 patients (34%) for massive GI bleeding, and the remaining for small bowel obstruction. The most common site was the small bowel (50%; n=19), median tumor size was 6.2cm (range, 1-20), and mitotic rate was higher than 5/50HPF in 39% of the tumors. Sixty-day mortality rate was 8% (n=3), postoperative complications occurred in 47% of the patients; these rates were significantly higher in comparison to the elective surgery matched cohort (p=0.03). Five- year RFS and OS rates for the study cohort were 65% and 74%, respectively; these did not differ from the survival rates calculated for the matched cohort of elective GIST patients. RFS and OS rates of patients treated for tumor rupture vs. massive GI bleeding or bowel obstruction were comparable (p>0.05). Conclusion: Overall, naïve GIST patients requiring emergency surgery have high risk tumors at initial presentation. Albeit emergency surgery is a risk factor for postoperative mortality and morbidity our data suggest that it is not an independent predictor of adverse long term outcome.

P162

An Elevated Neutrophil-to-Lymphocyte Ratio Portends a Poor Prognosis in Patients Treated with Microwave Ablation for Malignant Liver Tumors L.A. Shirley,* S.P. Albert, M. Bloomston, H. Khabiri, C. Schmidt. *The Ohio State University, Columbus, OH.*

Background: We have previously shown that the neutrophil-to-lymphocyte ratio (NLR), a marker for systemic inflammation, has prognostic value in liver malignancies treated with regional therapy. The aim of this study was to examine whether NLR is associated with outcomes in patients with primary and secondary liver malignancies treated with microwave ablation (MWA). Methods: The records of 128 patients treated with MWA for malignant tumors in the liver from any cause were reviewed. NLR was calculated from existing hematology lab work, and patients were excluded who did not have NLR values prior to and after MWA within six months. NLR > 5 was considered abnormal, and patients were stratified into four groups: NLR always less than 5,

NLR always greater than 5, NLR > 5 initially but normal after MWA and NLR initially normal but rises after MWA. Results: There were 76 patients with NLR evaluable at the time of MWA (34 colorectal cancer, 31 hepatocellular carcinoma, nine neuroendocrine tumor, three cholangiocarcinoma). The median age was 60.5 years and 72.4% were men. Patients who had an NLR less than 5 throughout had a significantly improved median overall survival (OS) compared to the other 3 groups (49.1 vs. 22.2, 22.5 and 26.4 months respectively, P=0.014) (see graph). There was no significant difference in progression-free survival (PFS) (11.8 vs. 13.6, 13.0 and 11.5 months respectively, P=0.518). Conclusion: An NLR less than 5 before and after MWA for primary or secondary liver tumors is associated with improved survival compared to having an increased NLR at any time. As such, patients with liver malignancies and an increased NLR may benefit from additional regional liver therapies or systemic therapy. Because there was no association with PFS, NLR may be more reflective of tumor biology than response to MWA or other therapy.



P163

Prognostic Features and Outcomes in Primary Liver Sarcoma
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Background: Primary liver sarcoma (PLS) is a rare and aggressive hepatic malignancy. Due to the low incidence of PLS, prognostic factors have not been well characterized. The purpose of our study was to evaluate survival outcomes in primary hepatic sarcomas and determine which factors predict survival. Methods: The Surveillance Epidemiology and End Results registry was used to identify patients with PLS from 1988-2009. Patients were evaluated by standard clinical and pathological indices including: age, gender, race, tumor size, tumor grade, histology, and extent of disease. Treatment related factors included surgery and radiation. Overall survival was assessed by Kaplan-Meier method. Univariate and stepwise multivariate Cox proportional hazards analyses were performed to identify prognostic factors. Results: 541 patients with PLS were identified. The mean age was 52 and most patients were male (55%) and white (75%). The most common histology type was blood vessel tumors (50.1%) followed by soft tissue neoplasms (17.7%) and complex mixed-stromal neoplasms (14.6%). Only 33% of patients underwent surgery and most (93%) did not receive radiation. When assessing outcomes, we observed median overall survival (OS) and cancer specific survival (CSS) of 6 months for the entire cohort. When stratified by treatment type, those who received surgery + radiation had the best survival (MS=97mos, p<.001) compared to those who received either radiation alone (MS=5mos) or no treatment (MS=2mos). Stepwise multivariate analysis showed that age, male gender, tumor size, advanced stage, and no surgery were independent predictors of worse survival, all p-values < .005. Conclusion: Primary liver sarcoma is an aggressive hepatic malignancy with low median OS of 6 months. Patients treated with surgery + radiation had the best outcome with a median survival of 97 months. Independent predictors for decreased survival included age, gender, tumor size, advanced stage, and no surgery.

P164

A Critical Analysis of Postoperative Morbidity and Mortality after Laparoscopic Radiofrequency Thermal Ablation of Liver Tumors
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Background: Although, the laparoscopic approach provides certain advantages over the percutaneous radiofrequency thermal ablation (RFA), the morbidity needs to be defined. The aim of this study is to analyze the morbidity and underlying risk factors after laparoscopic RFA of liver tumors. Methods: Between 1996- 2012, 910 patients underwent 1207 RFA procedures for malignant liver tumors in a tertiary academic center. Ninety-day morbidity and mortality were extracted from a prospective IRB-approved database. Statistical analyses were performed using regression, Student t and Chi-Square tests. Results: There were 578 men and 332 women. Tumor type included colorectal metastasis in 55% (n=502), hepatocellular cancer in 18% (n=160), neuroendocrine metastasis in 15% (n=133), and others in 13% (n=115). Complications occurred in 50 patients (5.5%) and were gastrointestinal in 13 patients (1.4%), infections in 10 (1.1%), hemorrhagic in 9 (1%), urinary in 7 (0.9%), cardiac in 4 (0.4%), pulmonary in 3 (0.3%), hematologic in 2 (0.2%) and neurologic in 2 (0.2%). The complication rates for an RFA done alone (5%) vs concomitantly with ancillary procedure (6%) were similar, p=0.6. Sixty seven percent of postoperative bleedings were from tumors located in the right posterior sector and required a laparotomy in 88%. Sixty percent of liver abscesses occurred in patients with a prior bilio-enteric anastomosis (BEA). The 90-day mortality was 0.4% (n=4). Hospital stay was 1.2±0.1 days and was prolonged to 4.4±0.3 days in case of complications. There was no effect of age, gender, tumor volume and type, underlying cirrhosis, ASA score, pre-operative chemo or radiotherapy on the incidence of postoperative complications. Conclusions: This study describes the morbidity and mortality to be expected after a laparoscopic RFA procedure. Our results show that additional caution should be used to prevent bleeding complications in patients with tumors located in the right posterior sector and infections in patients with a history of BEA. Morbidity was not increased when RFA was performed concomitantly with another surgical procedure, such as colorectal resection.

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Non-sentinel Node Status Sub-classified Prognosis of Patients with AJCC N2a Melanoma after Sentinel Node Biopsy and Completion Lymph Node Dissection
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Introduction. After completion lymph node dissection (CLND) for a positive sentinel node (SN) biopsy (SNB), about 20% of patients have further positive non-sentinel node (NSN). Status of the NSNs is a prognostic factor and has been suggested as a staging parameter. This study sought to investigate predictors of NSNs status and whether NSN status may improve AJCC staging system by sub-classify patients with N2a melanoma (2-3 positive lymph nodes) Methods. Retrospective data from patients with melanoma treated with SNB and CLND at 9 melanoma centers were gathered together in a multi-institutional database. Logistic regression analysis and Cox survival analysis were used to assess predictors of NSNs status and to adjust effect of NSNs status on patient prognosis. The concordance index (c-index) and the Akaike information criterion (AIC) were used for test post-estimation. Results. Of 1,660 patients who had a CLND, 23.4% had positive NSN(s). Patients with thicker [odds ratio (OR) 1.05, P=0.002] and ulcerated (OR 1.77, P<0.001) melanomas and with a greater number of positive SNs (OR 1.64, P<0.001) were at higher risk of NSNs involvement. Area under the receiver operating characteristic (ROC) curve was 0.664 (95%CI, 0.634-0.694). Median follow-up was 54 months (IQR 21-94). NSNs status was an independent predictor of survival [hazard ratio (HR) 1.26, P<0.001] after adjustment for age, gender, tumor thickness, ulceration and mitotic rate. Among patients AJCC stage N2 disease, NSNs status was able to sub-classify two groups at different risk of melanoma-related death after adjustment for patient age and sex, tumor thickness, ulceration and mitotic rate (HR 1.35, 95% CI 1.053-1.732, P=0.018). In this group, NSNs status improved the accuracy of the model (c-index and AIC of 0.72 and 894 versus 0.71 and 998 status, respectively). Conclusions. Patients with thicker and ulcerated tumors and more positive SNs were at greater risk of NSNs involvement. NSNs status

may be used to sub-classify patients with 2-3 positive lymph nodes (AJCC N2a stage).

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Sentinel Lymph Node (SLN) Biopsy in Patients with Thin (≤1 mm) Melanoma E.K. Bartlett,[1]* P. Gimotty,[2] A. Sinnamon,[1] H. Wachtel,[1] L.M. Schuchter,[4] M.E. Ming,[5] R. Elenitsas,[3] X. Xu,[3] D.E. Elder,[3] R.R. Kelz,[1] R.E. Roses,[1] B.J. Czerniecki,[1] D.L. Fraker,[1] G.C. Karakousis.[1] *1. Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA; 2. Department of Biostatistics, Hospital of the University of Pennsylvania, Philadelphia, PA; 3. Department of Pathology, Hospital of the University of Pennsylvania, Philadelphia, PA; 4. Department of Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA; 5. Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA.*

Introduction: SLN biopsy is the most sensitive method of staging patients with clinical stage I and II melanoma, however its role in patients with thin lesions (≤1 mm) remains controversial. Moreover, factors predictive of SLN positivity in this group have been variably reported. We examined a large cohort of patients with thin melanomas to better define predictors of SLN positivity. Methods: Between 1995-2011, 2047 patients with primary melanoma underwent SLN biopsy at our institution. 781 patients were identified with T1 melanomas and evaluable clinical and pathologic data. Predictors of SLN positivity were determined using univariate and multivariate regression analyses. Classification and regression tree (CART) analysis was used to risk-stratify patients for SLN positivity. Results: Of 781 patients who underwent SLN biopsy, 29 (3.7%) had nodal metastasis. By univariate analysis, mitotic rate (MR) (OR=1.22, p=0.005), thickness (OR=3.48, p=0.006), and Clark level IV/V (OR=4.08, p=0.003) were associated with SLN positivity. Lesions with lymphovascular invasion (N=7) or satellitosis (N=7) had a 29% SLN positivity rate. By multivariate analysis, MR (OR=1.2), thickness ≥0.75mm (OR=2.33), and level IV/V (OR=3.66) remained significant predictors of SLN positivity (p<0.0001) (Table1). CART analysis stratified lesions based on MR; MR<0.5 lesions (N=354) had a 0.6% SLN positivity rate versus 6.3% in ≥0.5 MR lesions (N=400). In patients with MR≥0.5 lesions, presence of level IV/V alone (N=193) or with thickness≥0.75 (N=136) increased SLN positivity rates to 9.3% and 10.3% respectively. In patients whose lesions had MR<0.5 and that were level II/III (N=192) or thickness<0.75 (N=215), the SLN positivity rate was 0%. With median follow up of 6.3 years, 6 SLN positive patients (21%) developed disease recurrence and 4 (14%) died of disease. Conclusion: The SLN positivity rate is low in patients with thin melanoma (3.7%) and exceedingly so in lesions with low MR (0.6%). Appreciable rates of SLN positivity can be identified, particularly in patients with mitoses, level IV/V, or tumors ≥0.75 mm in depth. These data can guide appropriate patient selection for SLN biopsy in patients with thin melanoma.

Logistic Regression Analysis (n=715*)

	Univariate		Multivariate Reduced		SLN Positivity
	OR	p-value	OR	p-value	
Thickness					
0.01-0.74 mm	1.00	---	1.00	---	1.8%
0.75-1.00 mm	3.48	0.006	2.33	0.070	5.7%
Mitotic Rate - Continuous	1.22	0.005	1.2	0.017	---
Clark Level					
II/III & Unk	1.00	---	1.00	---	1.8%
IV/V	4.08	0.003	3.66	0.008	6.1%
Regression					
Present	0.65	0.440	---	---	2.4%
Not Present	1.00	---	---	---	4.1%
TILs					
Absent	1.01	0.980	---	---	3.6%
Not Absent	1.00	---	---	---	3.7%
Sex					
Male	1.29	0.531	---	---	3.9%
Female	1.00	---	---	---	3.4%
Site					
Trunk/Head and neck	0.73	0.416	---	---	3.1%
Extremity	1.00	---	---	---	4.6%
Mitotic Rate - Binary**					
<0.5	1.00	---	---	---	0.6%
>=0.5	12.55	0.001	---	---	6.8%
Ulceration					
Present	No events were ulcerated				0%
Not Present					3.9%

*This is the set where mitotic rate is known.
** This is the cutpoint based on CART analysis.

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Pathology Review for Melanoma Patients Referred to a Melanoma Treatment Center Significantly Impacts Diagnosis and Management M. Niebling,* L. Haydu, R. Karim, J. Thompson, R. Scolyer. *Melanoma Institute Australia, Sydney, NSW, Australia.*

Introduction An accurate and comprehensive pathology report is essential for treatment and follow-up of patients with melanoma. However, pathologists sometimes disagree on the diagnosis of melanoma or its histopathologic features. Consequently, patients referred to many major melanoma treatment centers for management after a melanoma diagnosis has been made routinely have their pathology slides re-evaluated by treatment center pathologists. This study sought to determine if staging and management of melanoma patients significantly changed as a consequence of central pathology review. Methods 5253 external and internal pathology reports were reviewed. From each report, the following were determined: diagnosis, American Joint Committee on Cancer (AJCC) T-stage, appropriate excision margins and whether or not sentinel lymph node (SLN) biopsy (SLNB) would be recommended on the basis of the report (the latter two according to published guidelines). Differences in diagnosis, T-stage and management recommendations based on the external and internal reports on the same specimen were analyzed. Results Diagnosis of melanoma changed in 8.6% of cases after review. Where both pathologists agreed on invasive melanoma, T-stage changed in 19.8% after review. Surgical management changed in 13.8% and a recommendation for SLNB changed in 9.9%. Internal reports contained the essential criteria for determining T-stage, surgical management and recommendations for SLNB in 97.2%, 99.6% and 99.3% of reports. External reports contained these criteria in 87.2%, 95.4% and 94.7% (each p<0.001). Conclusion Diagnosis, T-stage and management recommendations often change following pathology review at a specialist melanoma treatment center. We recommend that pathology review be considered for all patients referred to such centers for management or advice.

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Prognostic Significance of Tumor Mitotic Rate in Intermediate Thickness Melanoma Staged with Sentinel Lymphadenectomy M.O. Meyers,* J. Baker, J. Frank, K. Stitzenberg, D.W. Ollila. *Surgery, University of North Carolina School of Medicine, Chapel Hill, NC.*

Introduction: Tumor mitotic rate (TMR) is an important prognostic variable in thin melanoma. However, data are lacking as to the significance of TMR in clinically node-negative intermediate thickness melanoma staged with sentinel lymphadenectomy (SLN). Methods: A prospective single-institution database was reviewed. Patients with intermediate thickness (Breslow depth 1.01-4.00mm) undergoing sentinel lymph node biopsy who had mitotic rate reported were included. TMR was categorized as <1 (low TMR) or ≥ 1/mm2 (High TMR). Associations were examined using Fishers's exact test. Results: 489 patients met criteria (313 T2). 77 were SLN positive (34 T2). TMR was not associated with a positive SLN in all patients or in T2 or T3 subsets (P= 0.08, 0.28 and 0.55 respectively). High TMR tumors were more likely to recur than low TMR tumors (26.9% vs. 7.3%; p=0.0001) High TMR was associated with greater risk in T2 (17.4% vs. 4.0%; p=0.0001) than T3 (36.8% vs. 20.9%; p=0.06) tumors. High TMR increased recurrence risk in both SLN negative (23.1& vs. 5.7%; p=0.001) and SLN positive (44.9% vs. 17.9%; p=0.02). High TMR was also associated with increased recurrence risk in both ulcerated and non-ulcerated tumors. (Table) Conclusions: High TMR is a powerful risk factor for recurrence in intermediate thickness melanoma. Risk was increased in both SLN positive and negative tumors and in ulcerated and non-ulcerated tumors, with the exception of SLN positive, ulcerated lesions. These data may be useful in stratifying recurrence risk and follow-up in intermediate thickness melanoma and selecting patients for adjuvant therapy.

Group	N	High TMR Recurrence Risk	Low TMR Recurrence Risk	P
SLN Negative, Non-Ulcerated	293	20.1%	5.2%	0.0001
SLN Negative, Ulcerated	107	29.5%	10.3%	0.04
SLN Positive, Non-Ulcerated	43	45.8%	5.2%	0.005
SLN Positive, Ulcerated	30	42.1%	27%	0.47

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The Role of Intralesional Interleukin-2 for In-Transit Melanoma: A Validation Study S. Hassan,[1]* T. Petrella,[1] S. Kamel-Reid,[2] A. Al Habeeb,[2] D. Ghazarian,[2] F. Wright.[1] *1. Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 2. University Health Network, Toronto, ON, Canada.*

Introduction: About 5-20% of patients with melanoma will develop in-transit disease and approximately 56% will develop distant metastases. Although there are several modalities being used for the treatment of in-transit disease, intralesional interleukin-2 (IL-2) is a safe therapeutic injection that can be easily administered in the office. The use of IL-2 has been previously reported in a series of 49 patients by Temple's group in London, Ontario. They found a complete response in 51%, a partial response in 31%, and no response in 18% of patients. Methods: We performed a retrospective review of all melanoma patients who received intralesional interleukin-2 for in-transit disease at our institution since 2009. Patients were injected with IL-2 over an 8-16 week time frame up to 8 times every 2 weeks. All patients had a biopsy 8-10 weeks after completion of IL-2 to confirm pathologic response. We identified 29 patients in total and extracted clinico-pathological variables. Survival analysis was performed using STATA. Results: The mean age of our patient cohort was 67 years (range; 28-91 years). The lower extremity was the most frequent site for in-transit disease, in 26/29 patients. The mean follow-up for our cohort since the start on IL-2 treatment was 12.3 months. 46% of the patients had a complete clinical response (13/28 patients), of which 11/13 patients had a complete pathologic response. 36% (10/28) of patients had a partial response, and 18% of patients (5/28) demonstrated progressive disease with IL-2 treatment. 2/23 patients with a partial or complete response died from melanoma, and 2/5 patients with progressive disease also died. The mean time to death was longer amongst patients who responded, 14.6 months, versus 5.1 months in patients with progressive disease. The overall survival for patients with progressive disease was worse than for patients who demonstrated a partial or complete response (P = 0.02) Conclusions: Intralesional IL-2 results in partial or complete response in 82% of patients. Our results are comparable to those reported previously, suggesting that IL-2 is an effective local treatment for patients with in-transit disease.

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In Transit Sentinel Lymph Nodes in Cutaneous Melanoma – Treatment and Recurrence Patterns M.R. Forster,* J.L. Weber, J.L. Messina, A.A. Sarnaik, V.K. Sondak, J. Zager, C.A. Puleo. *Surgical Oncology, H. Lee Moffitt Cancer Center, Tampa, FL.*

INTRODUCTION: In transit sentinel lymph nodes (SLN) are any sentinel nodes located between a primary cutaneous melanoma and a major nodal basin (cervical, axillary or ilioinguinal), inclusive of minor basin (popliteal or epitrochlear) lymph nodes. The management of such nodes and their upstream major basins is an area of controversy. METHODS: We performed a retrospective review of all patients (pts) treated at our institution with in transit SLNs and melanoma from 1994-2012. Patients were analyzed for tumor and SLN characteristics, treatment of nodal metastasis, and recurrence patterns. RESULTS: In transit SLNs identified by preoperative lymphoscintigraphy or SPECT scan were resected from 199 pts during the study period. The median age was 63 years, 58% were male, median Breslow depth was 1.6mm, and median follow up was 18.4 months. 28 pts (14%) had metastatic melanoma to an in transit SLN, 9 of these pts (4.5%) also had a positive major basin SLN. Treatment of pts with a positive in transit SLN included minor basin completion lymphadenectomy (CL), observation, local radiotherapy, systemic therapy, and clinical trials (see Table 1). Of the 28 pts with in transit nodal disease, 13 recurred (46%). 6 of these were in transit "basin" recurrences, all of whom had positive SLNs from those locations. Only 1 of the pts had received additional minor nodal basin CL. Distant recurrence occurred in 3 (10.7%), and regional recurrence in 4 (14.3%), all 4 of whom had positive major basin SLNs, and 3 of whom had CL. In pts with positive in transit SLNs, 68% of the time it was their only site of metastatic disease, and none of these pts had a major basin recurrence. CONCLUSIONS: In transit SLNs were positive 14% of the time consistent with published rates of major basin SLN positivity, thus when identified preoperatively should be resected. Patients with positive in transit SLNs have a significant risk of recurrence (46%), including at the site of the in transit SLN biopsy. Management of upstream major basins should take into account lymphatic drainage patterns, and further collaborative multi-institutional research is needed to determine the necessity of CL in a negative upstream basin.

Table 1. Treatment and recurrence patterns in 28 melanoma pts with metastatic in transit SLNs (CLND = completion lymph node dissection)

Treatment Type	NO recurrence	Local recurrence	In transit recurrence	Regional recurrence	Distant recurrence
Clinical Trial (n=5)	1		2	1	1
Observation (n=7)	6		1		
Major Basin CLND (n=5)	1		1	1	2
Major basin and in transit CLND (n=2)	1		1		
Sytemic Tx (n=3)	1		1	1	
Unknown (n=5)	4			1	
Local radiation (n=1)	1				
Totals (% of n=28)	15(54%)	0(0%)	6(21%)	4(14.3%)	3(10.7%)

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Termination of BRAF Targeted Therapy Augments Tumor Growth in the Setting of Vemurafenib Resistance M.E. Lidsky,* R.S. Turley, P. Speicher, C.K. Augustine, F. Ali-Osman, D.S. Tyler. *Duke University, Durham, NC.*

Introduction: Although the majority of melanoma patients harboring the activating V600E BRAF mutation respond to targeted therapy, the duration of response is short lived. There is considerable debate regarding the role of maintenance therapy, the theory being that cessation of targeted agents may promote aggressive tumor behavior. We therefore sought to define the effect of vemurafenib at varying concentrations on cells determined to be resistant to this drug. Methods: Vemurafenib resistance to the ATCC melanoma cell line A375 (V600E BRAF mutant) was generated by continuous exposure to increasing concentrations of vemurafenib in vitro. Real time cell sensing technology was utilized for dose response experiments, which allowed for determination of the inhibitory concentration at which 90% of the cell population survived (IC10). In addition, the melanoma cell line A2058 (V600E BRAF mutant) was identified from a panel of melanoma cell lines never exposed to vemurafenib to be inherently resistant to vemurafenib. Results: A375 cells induced to be resistant by chronic exposure to vemurafenib (A375rVem) were found to have an IC10 of 3μM vemurafenib compared to the parent A375 cell line that has an IC10 of 0.05μM. The intrinsic IC10 of A2058 never exposed to vemurafenib was similarly 3μM. In real time dose response experiments with A375rVem, doses of vemurafenib below the IC10 augmented growth, indicated by the greater slope of the exponential growth phase (Figure 1a). This finding was surprisingly also observed in the inherently resistant A2058 melanoma cell line. Complete cessation of vemurafenib exposure to A375rVem also resulted in enhanced cell population growth (Figure 1b). Conclusion: These studies demonstrate that as vemurafenib resistance develops, low dosages of this drug may actually augment tumor growth. Furthermore, withdrawal of drug from these tumors also appears to increase proliferation. These observations highlight the complexity of optimal treatment strategies using targeted agents in BRAF mutant tumors as resistance develops, and may suggest the necessity for maintenance therapy.

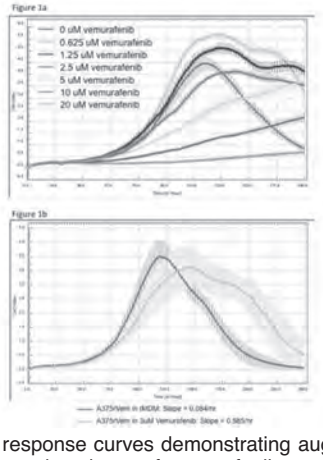

Figure 1a: Dose response curves demonstrating augmented proliferation of A375rVem at low doses of vemurafenib.
Figure 1b: Termination of vemurafenib therapy results in augmented proliferation in the setting of induced vemurafenib resistance.

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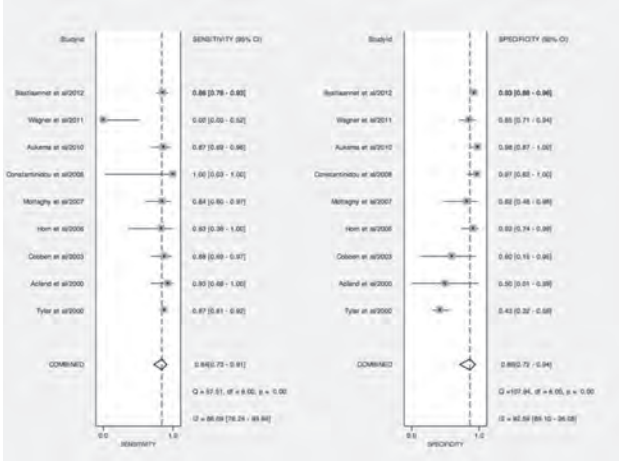
Value of Positron Emission Tomography Scan in Stage III Cutaneous Melanoma: A Systematic Review and Meta-Analysis A.M. Rodriguez Rivera,[1]* A. Ramjaun,[2] H. Alabbas,[1] A. Meguerditchian.[1] *1. McGill University Health Centre, Montreal, QC, Canada; 2. McGill University Clinical and Health Informatics, Montreal, QC, Canada.*

INTRODUCTION: The objective of this study is to review the collective experience of PET scan in the detection of systemic metastases in patients with stage III cutaneous melanoma. METHODS: Medline, Embase, PubMed, Ovid, Scopus, Cancerlit and Web of Science online databases were systematically searched for relevant studies performed between January 1, 1990 and June 30, 2012. We included English language reports that evaluated cutaneous melanoma patients with stage III disease, with at least 10 patients and reported statistical data to assess PET in the detection of distant metastasis. The SIGN diagnostic accuracy study assessment tool was used to evaluate publication quality and a meta-analysis was performed using Stata statistical software to quantify the clinical utility of the PET scan. RESULTS: Nine studies (6 retrospective and 3 prospective) were included in the meta-analysis with a total of 583 patients. On a 9-point scale, the mean quality score was 4.33. Weighted mean age at the time of initial staging was 53.4 years old (range 16 – 93) and male to female ratio was 1.3:1. Initial stage was T1-4N1-3M0 in 78.6% (458/583) of patients, 16.3% (95/583) T1-4N-2M0 and 5.1% (30/583) T2-4N1-3M0. Collectively, the pooled sensitivity was 0.84 (0.73 - 0.91) and the pooled specificity was 0.86 (0.72 - 0.94). Based on a summary ROC curve analysis, the overall area under the curve for PET was 0.91 (0.88 - 0.93) with a DOR of 32.71 (11.00 - 97.25). A change in stage and/or management was noted in 22% (128/583) of patients when PET was utilized, 29% (94/323) when patients specifically had a clinically palpable and pathological positive regional node(s). CONCLUSIONS: The findings of this review indicate that PET may be useful in detecting distant metastases in patients with stage III cutaneous melanoma. For this group of highly selected patients, PET has a high sensitivity, specificity and performance frequently leading to a change in treatment plan.



Cumulative sensitivity and specificity of PET scan in stage III cutaneous melanoma

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XPO1 and BRAF Inhibition Synergize and Modulate pRb, Survivin and ERK in Melanoma R.A. Salas Fragomeni,* J.C. Cusack. *Harvard Medical School / Massachusetts General Hospital, Boston, MA.*

Introduction: BRAF kinase activating mutations drive the proliferation of at least half of all melanomas. The targeting of these activated BRAF kinases by BRAF inhibitors has achieved outstanding clinical results for patients harboring a BRAF mutation. However, resistance to BRAF inhibitors has limited the duration of response. Melanoma's multi-drug resistance has been associated to apoptosis evasion and anti-growth signaling insensitivity. XPO1-mediated nuclear export modulates the function of several proteins which have a role in melanoma's ability to proliferate and evade apoptosis. Therefore, the inhibition of XPO1 could enhance the response to current BRAF inhibitors and overcome the associated resistance. Methods: Studies were done using human malignant melanoma cell lines. KPT-185 was used for XPO1 inhibition. BRAF inhibition was achieved by PLX4032. MTT assays were used to evaluate cell proliferation. FACS analysis with annexin/PI staining was used to measure cell cycle and cell death. Synergy was determined by Chou-Talalay method. Treatment effects on cleaved caspase-3, PARP cleavage, TP53, pRb and Survivin were analyzed by western blot. Xenograft models where used to evaluate in-vivo response. Results: Our studies show that XPO1 inhibition decreases melanoma cell proliferation independent of BRAF mutation status and synergistically enhances the effects of BRAF inhibition on BRAF-mutant melanoma by promoting cell cycle arrest and apoptosis. In melanoma xenograft models, XPO1 inhibition reduced tumor growth independent of BRAF or NRAS status and induced complete regression of BRAF V600E tumors when combined with BRAF inhibition. Mechanistic studies show that XPO1 inhibition was associated with p53 stabilization, and pRb and Survivin modulation. Furthermore we found that BRAF inhibition abrogates ERK phosphorylation associated with XPO1 inhibition, and contributed to the synergistic response in the BRAF mutant melanoma cell lines. Conclusion: XPO1 inhibition synergizes with BRAF inhibition and their combination could be used to overcome intrinsic and acquired resistance mechanisms to BRAF inhibitors in BRAF mutant melanoma.

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Bio-Impedance Spectroscopy Measurement of Melanoma Patients Undergoing Axillary Sentinel Lymph Node Biopsy M. Kovarsky, P. Beitsch,* T. Huber. *Dallas Surgical Group, Dallas, TX.*

IIntroduction: Sentinel Lymph None Dissection (SLND) removes the lymph node(s) that drain a primary melanoma. The removal of these lymph nodes can lead to an increase in extracellular fluid (ECF) which could result in lymphedema even years after the surgery. The extremity's resistance to electrical current will vary with the amount of extracellular fluid (ECF). This resistance can be measured by bioimpedance spectroscopy (BIS) and recorded as a number (L-Dex score). Previous studies in breast cancer have shown that an absolute value >10 or a change of >10 from baseline indicates a significant increase in ECF. This analysis was performed to evaluate whether BIS is helpful in melanoma patients and to compare the risk of increased ECF in extremity versus trunkal melanomas. Methods: We performed a retrospective study of 148 melanoma patients from Jan 2010- June 2012 who had wide excision and axillary sentinel lymph node biopsy - 73 with a trunkal primary and 75 with an arm primary. Wide excisions were closed with advancement flaps (trunkal 72/73; extremity 58/75) or skin grafts (trunkal 1/73; extremity 13/75). BIS measurements were taken pre-operatively (or at first visit after initiation of the BIS program-January 2010) and then every 3-6 months. Results: Patients with a trunkal primary had a higher number of sentinel nodes removed (4.0) compared to arm primaries (2.7) P<0.05. There was no difference in the percentage of patients with trunkal vs arm primaries who developed increased ECF; however when patients were divided by type of primary closure, the patients with arm primaries and a skin graft had a significantly great chance of increased ECF compared to trunkal or arm primaries closed with advancement flaps. This difference was independent of age, gender, BMI, and number of sentinel nodes removed. No patients developed clinical lymphedema during this study. Conclusions: BIS appears to be effective at detecting pre-clinical increase in extracellular fluid in melanoma patients undergoing wide excision and SLND. Patients who require a skin graft to close their wide excision should be carefully monitored to detect increased extracellular fluid.

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Serum S-100B Levels are Associated with Non-Sentinel Node Positivity in 68 Sentinel Node-Positive Melanoma Patients K.P. Wevers,* S. Kruijff, M.J. Speijers, E. Bastiaannet, A.C. Muller Kobold, H.J. Hoekstra. *UMCG Groningen, Groningen, Netherlands.*

Background. Completion lymph node dissection (CLND) in sentinel node (SN)-positive melanoma patients leads to substantial morbidity and costs, while only about 1 out of 5 patients have a metastasis in non-sentinel nodes (NSNs). The aim of the present study was to investigate if biomarkers Lactate Dehydrogenase (LDH) and S-100B in SN-positive patients are associated with NSN positivity and thus might identify patients in whom CLND could be omitted. Methods. All SN-positive patients who underwent CLND at a single institution between 2004 and mid-2012 were analyzed. Serum LDH and S-100B values measured the day before CLND were tested for

their association with NSN-positivity. Both the reference cutoff of our institution and an optimal cutoff determined by receiver operating characteristic analysis were tested for their association with NSN positivity. Results. A positive NSN was found in 16 of the 68 patients (23.5%) undergoing CLND. Univariate analysis revealed Breslow thickness (p=0.04), number of positive SNs (p=0.02), proportion of involved SNs (p=0.04), size of largest metastasis in SLNB (p=0.009), and S-100B value (p=0.001) to be associated with NSN positivity. LDH level was not significantly associated with NSN positivity (p=0.11). S-100B with an obtained optimal cutoff of 0.07 μg/l was a significant independent predictor for NSN positivity in multivariable analysis (OR 8.88; p=0.006). When categorized based on NSN status, for 120 healthy individuals, 52 NSN negative melanoma patients, and 16 NSN positive melanoma patients, the median S-100B levels were 0.07 (range 0.01-0.59), 0.05 (range 0.02-0.14), and 0.09 (range 0.02-1.65), respectively (p=0.001). NSN negative patients showed lower S-100B levels (p=0.03), and NSN positive patients showed higher levels compared to healthy individuals (p=0.008). (Figure 1) Conclusion. The results of this study show that S-100B with a cutoff within the reference interval could improve NSN risk scores to select SN positive patients in whom CLND could safely be omitted in the future.

Figure 3. Comparison of S-100B levels in healthy individuals and SN positive melanoma patients according to NSN status

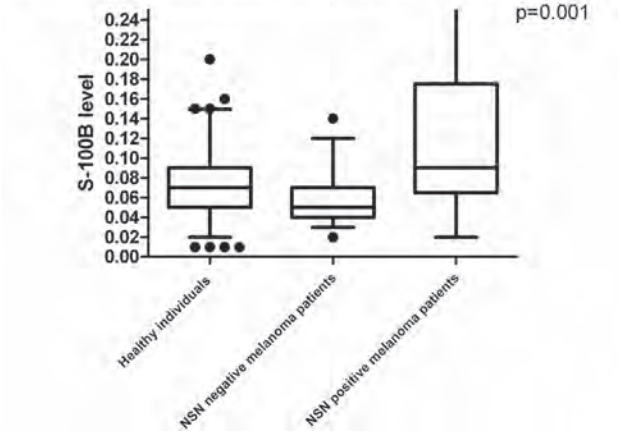

Figure 1. Comparison of S-100B levels in healthy individual and SN-positive melanoma patients according to NSN status.

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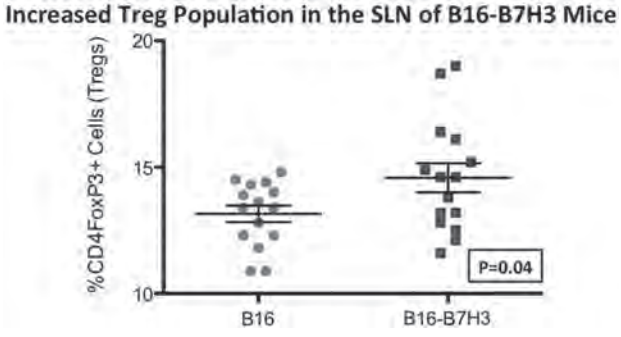
Tumor B7H3 Expression Affects the Immunologic Milieu of Sentinel Lymph Nodes D.M. Bello,* K. Kreymborg, J.P. Allison, C.E. Ariyan. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: The sentinel lymph node (SLN) remains the most important prognostic factor in the survival of melanoma. While work has shown that the SLN is a relatively immunosuppressed site, with an increased expression of T regulatory cells, decreased antigen presenting cells, and a decreased cytotoxic environment, the mechanisms by which this occurs remain unclear. Prior analysis of patients with melanoma identified an increased expression of B7H3 in the SLNs of patients who died of disease. The goal of this study was to analyze the effect of B7H3 expression on tumor growth and the SLN. Methods: B16 melanoma cells were transduced with B7H3 or control. Mice were injected intradermally on Day0 with $5x10^6$ cells on the left flank. Mice were sacrificed on Day 9 and Day 17. Inguinal draining (SLN) and non-draining (NSLN) lymph nodes were analyzed for cell populations by flow cytometry. The metastasis rate was calculated by RT-PCR for tyrosinase-related protein 1 (TYRP-1). Experiments were repeated three times and data was pooled. Differences between groups were calculated by t-test. Results: Transduction of B7H3 to the B16 melanoma cell line was confirmed by flow cytometry. There was no detectable expression of B7H3 on the control B16 cell line. Expression of B7H3 on B16 melanoma cells did not affect the primary tumor growth rate, or the rate of metastasis to the sentinel lymph node. When the SLNs from the mice with tumors expressing B16-B7H3 were compared to the control B16 SLNs, an increased T regulatory component, and a decreased macrophage and dendritic cell component were found (see Image). This is in contrast to the NSLN, which did not demonstrate any difference in the T regulatory cell population between mice with a B16 or B16-B7H3 tumor. Conclusions: This study suggests that B7H3 expression affects the immunophenotype of a SLN. In mice with tumors expressing B7H3, the SLN has a decreased percentage of antigen presenting cells, and an increased expression of T regulatory cells, which is independent of tumor metastasis rate. This data supports the further development of antibodies that target immunomodulatory molecules such as B7H3.



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Single Photon Emission Computed Tomography (SPECT) Compared with Conventional Planar Lymphoscintigraphy (LS) for Preoperative Sentinel Node Localization in Cutaneous Malignancies M. Yamamoto,* M. Djulbegovic, J. Montilla-Soler, E. Eikman, R.J. Gonzalez, C.W. Cruse, A.A. Sarnaik, V.K. Sondak, J. Zager. *H. Lee Moffitt Cancer Center, Tampa, FL.*

Introduction: Accurate pre-operative lymphoscintigraphy is vital to performing a sentinel lymph node biopsy (SLNB). Potential advantages of SPECT LS over conventional planar LS are the ability to more readily identify aberrant drainage patterns such as interval nodes as well as provide the surgeon anatomical landmarks not seen in planar LS. Methods: Retrospective review comparing SPECT and planar LS for patients (pts) with cutaneous malignancies. Results: Planar and SPECT LS images were obtained in 99 consecutive pts (median age 64, range 8-87) with cutaneous malignancies (melanoma =86, Merkel=7, squamous =2, and other cutaneous malignancies =4) after intradermal injection of technetium-99m sulfur colloid (median dose 290 mCu). Since SPECT LS is typically performed for pts considered to be at high risk for aberrant drainage, there was a large population of head/neck (61%) and truncal (24%) pts. The mean number of nodes identified on SPECT LS was 3.17 compared to only 2.61 on planar LS (p<0.0001). Forty-nine pts (49.5%) had concordant imaging between SPECT and planar LS, 39 pts (39.4%) had additional sites of nodal drainage seen on SPECT when compared to planar imaging, and 11 pts (11.1%) additional sites of drainage were seen on planar imaging when compared to SPECT. In 5 pts (5%) both SPECT and planar LS failed to identify a node. In an additional 3 pts (3%), SPECT failed to identify nodes seen on planar LS and in 2 pts planar LS (2%) failed to identify SLNs seen on SPECT. Conclusions: SPECT LS may be a useful adjunct to planar LS and could help with localization of SLNs for cutaneous malignancies. It demonstrates additional SLNs otherwise not seen on planar LS in almost 40% of pts. Since planar LS will identify SLNs not seen on SPECT in 11% of pts, we recommend both modalities especially when ambiguous or multiple drainage patterns can occur such as head and neck, mid truncal and lower buttock lesions where direct pelvic drainage may be seen. Long term follow-up will be required to validate that identification of additional nodes is clinically significant.

		Nodes visualized by SPECT			Nodes Visualized by Planar			# Sentinel lymph nodes obtained		
	# patients (n)	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Head/Neck	61	3.20	3.00	0-8	2.79	3.00	0-8	3.45	3.00	0-12
Trunk	24	2.96	3.00	0-6	2.21	2.00	0-6	3.00	3.00	0-9
Upper Extremity	3	4.00	4.00	3-5	3.00	3.00	3	2.00	3.00	0-3
Lower Extremity	9	3.44	4.00	1-5	2.33	2.00	1-4	2.44	2.00	1-6
Genitalia	2	2.50	2.50	1-4	2.50	2.50	1-4	3.00	3.00	3
Total	99	3.17	3.00	0-8	2.61	2.00	0-8	3.20	3.00	0-12

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Neuropathic Pain Following Wide Local Excision and Sentinel Node Biopsy for Melanoma: An Undiagnosed & Significant Problem C.H. Thomson,* J. Garioch, M. Moncrieff. *Norfolk and Norwich University Hospital, Norwich, United Kingdom.*

Standard care for invasive melanoma is surgical and post-operative pain can transform into the debilitating complex regional pain syndrome (CRPS). The aim of this study was to ascertain the prevalence of neuropathic pain in these patients and evaluate impact on quality of life. This was a prospective, cross-sectional study where questionnaires were administered to 100 consecutive patients attending clinic. All patients had undergone wide local excision (WLE) and a negative sentinel lymph node biopsy (SLNB) (AJJC stage I or II). The questionnaire consisted of a neuropathic pain tool (painDETECT) and a melanoma quality of life tool (FACT-M). The median age was 64 years (range 22-85). Twenty-six (26%) patients reported pain with 8% reporting intermediate to severe neuropathic pain and 2% described CRPS. The age of patients experiencing pain at their melanoma site was significantly lower than those who did not have pain (p=0.011, median 59.5 v 65 years). Patients with a melanoma site on a limb had significantly higher pain scores than those located axially (p=0.011). Pain scores were inversely correlated with quality of life scores, with patients scoring intermediate to high pain score achieving a significantly lower FACT-M quality of life score (p=0.002). Importantly it was also shown that pain scores were not related to number of months since surgery. This study demonstrated that post-operative pain was an issue for 1 in 4 patients following WLE & SLNB and that this was a chronic problem. Younger patients and those with a limb melanoma were more likely to experience post-operative pain with a significant negative impact on quality of life. This is particularly worrying since this cohort is more likely to consist of independently mobile patients of working age and the adverse socio-economic impact of chronic post-operative pain could be devastating. This evidence has direct implications for current, international melanoma practice and highlights the need to assess post-operative pain and refer early to appropriate pain services. A trial investigating potential peri-operative intervention to prevent post-operative neuropathic pain is merited.

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Outcome after Resection of Limited Residual or Progressive Disease in Metastatic Melanoma Patients Treated with B-RAF Molecular Targeted Therapy R.A. Snyder,* R. Kauffman, I. Puzanov, J. Sosman, M.C. Kelley. *Vanderbilt University School of Medicine, Nashville, TN.*

Introduction: B-RAF inhibitors induce anti-tumor responses and improve survival of patients with B-RAF mutation-positive metastatic melanoma. In most patients, resistance develops within several months, limiting the long-term benefit of these drugs. The purpose of this study was to evaluate whether resection of residual or progressive disease improves tumor response and survival of these patients. Methods: A retrospective chart review of 84 patients who received B-RAF targeted therapy between 2007 and 2011 was performed, and 20 patients who underwent surgical resection of limited residual or progressive disease while receiving therapy were identified. Records were reviewed for demographics, pathology, and clinical characteristics, as well as overall and progression-free survival after initiation of targeted therapy. Results: Table 1 summarizes the demographic, clinical, and outcome measures for our group compared to two pivotal studies of B-RAF targeted therapy in metastatic melanoma (REF 1-2). A total of 29 resections were performed in these 20 patients while on B-RAF targeted therapy. The group's demographics, metastatic stage at time of treatment, and disease-free interval were comparable to these studies. A partial or complete response was seen in 100% of patients versus 48-53% in other studies. Overall survival (OS) at 6 months was 100%, compared to 77-84% in other studies. OS at 12 months was 84% (95% CI, 59%-95%). Median progression free survival (PFS) was 9.8 months, compared to 5.3 and 6.8 months in other studies. Patients in this group remained on drug for a median of 14 months compared to 6 to 7 months in other reports. Conclusions: Resection of isolated residual or progressive disease in highly selected patients receiving B-RAF targeted therapy was associated with a longer duration of drug treatment and increased PFS and OS compared to patients who did not undergo surgery. A prospective trial of surgical resection compared to second-line systemic therapy is being considered. References: 1: Sosman NEJM 2012; 366:707-14. 2: Chapman NEJM 2011; 364:2507-16.

Characteristic	Current study	Sosman 1	Chapman 2
Number (n)	20	132	337
Median age (range)- yrs	52.5 (28-67)	51.5	56 (21-86)
Male sex - no. (%)	13 (65)	81 (61)	200 (59)
M stage- no. (%)			
M1a	5 (25)	33 (25)	34 (10)
M1b	1 (5)	18 (14)	62 (18)
M1c	14 (70)	81 (61)	241 (72)
Complete or partial response- no. (%)	20 (100)	70 (53)	106 (48)
Progression-free survival (PFS) (mos)	9.8	6.8	5.3
Overall survival at 6 months (%)	100	77	84

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Location and Significance of Positive Nonsentinel Lymph Nodes in Head and Neck Melanoma D.E. Gyorki,[1]* J.O. Boyle,[1] G. Ian,[1] L. Morris,[1] A.R. Shaha,[1] B. Singh,[1] R.J. Wong,[1] J.P. Shah,[1] K. Busam,[1] D. Kraus,[2] D.G. Coit,[1] S.G. Patel.[1] *1. MSKCC, New York, NY; 2. North Shore-LIJ Cancer Institute, New York, NY.*

Introduction The complex anatomy and lymphatic drainage patterns in the head and neck pose unique challenges for sentinel lymph node biopsy (SLNB) for melanomas in this region. This study describes the incidence, location and implications of positive nonsentinel lymph nodes (NSLN) in patients with cutaneous head and neck melanoma. Methods A retrospective chart review was performed using a single institution prospectively maintained melanoma database. Patients were included if they had a melanoma in the head or neck with a positive cervical SLN and underwent completion lymphadenectomy. The lymphadenectomy specimen was divided in the operating room into lymph node levels I-V, each of which was analyzed separately. Categorical variables were compared using the Chi Squared test, and estimates of survival distribution differences were compared using the log rank test. Results Of 387 melanoma patients who underwent successful cervical SLNB, 54 had at least one positive node identified (14%). Thirty six patients (67%) underwent immediate completion lymphadenectomy (CLND) of whom eight patients (22%) had a total of 20 positive NSLN's. Of the 20 positive NSLNs identified, ten (50%) were in the same lymph node level as the SLN and seven (35%) were in an immediately adjacent level; only three positive NSLNs (15%) in two patients were found in a non-adjacent lymph node level. The only factor predictive of NSLN positivity was size of the tumor deposit in the SLN > 0.2mm (p=0.04). The rate of nodal failure after CLND was 11.1% (12.5% with positive NLSN and 10.7% after negative NSLN, p=0.65). Conclusions This study demonstrates that after a positive SLNB in the neck, the NSLN positive rate is 22%. Furthermore, the majority of positive NSLNs are found within the same nodal level as the sentinel node or immediately adjacent to it.

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Isolated Limb Infusion for Melanoma In-Transit Metastases: Expe-rience at Two Canadian Centres L. Chin-Lenn,* C. Temple-Oberle, J. McKinnon. *Tom Baker Cancer Centre, Calgary, AB, Canada.*

Introduction The management of melanoma in-transit metastases (ITM) is challenging. Isolated limb infusion (ILI) is a minimally invasive technique that delivers low-flow chemotherapy to an affected extremity. This study describes the experience of the two initial Canadian centres to adopt this technique. Method Prospective databases identified 53 consecutive patients who had 55 ILI procedures from 2002-2012. Patient demographics, tumor characteristics, procedural information, complications and response were extracted from charts. Response was measured using the response evaluation criteria in solid tumors (RECIST). Results Of 53 patients, 64% were female with mean age 69 (range 27-90) and lower limb involved in 45 (85%). All had negative staging prior to procedure except one who declined. Median time from diagnosis of ITM to ILI was 4 months (range 1-87 months). Non-surgical treatments were used prior to ILI in 24 patients including radiation (8), chemotherapy (2), interferon (9), isolated limb perfusion (2) and intralesional interleukin-2 injection (2). One procedure was aborted due to brachial artery vasospasm. Two patients had repeat ILI for progressive disease. In total, 54 ILIs were performed using either melphalan and actinomycin-D for 30 minutes (9) or single-agent melphalan for 15 minutes (20) or 30 minutes (25). Doses were calculated with volume-displacement technique (32), circumferential measurements (21) with 2 doses estimated due to failed volume-displacement. Wieberdink toxicity was grade 1 and 2 in 60%, 3 in 26% and 4 in 13%. Median follow up was 17 months. The overall response rate was 63% (29% complete response (CR), 33% partial response (PR)) for a median duration of 9 months (11 months in the CR

group). Stable disease (SD) occurred in 22% for a median of 10 months. Progressive disease (PD) occurred in 16%. Of those with PR or PD, 6 were converted to CR using other modalities post ILI (radiation, resection, aldara, ipilimumab). Median survival in all patients was 25 months. Conclusion ILI may result in remission for melanoma ITM but importantly also may slow disease progression either alone or in combination with other modalities post ILI.

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Interobserver Variation and Completeness of Pathology Reporting for Melanoma Between 2001 and 2011 in New South Wales, Australia: An Analysis of 4924 Cases M. Niebling,* L. Haydu, R. Karim, J. Thompson, R. Scolyer. *Melanoma Institute Australia, Sydney, NSW, Australia.*

Introduction Pathology reports are critically important for conveying information to clinicians who must make important management decisions for their patients. This study sought to assess, in a large cohort of patients with primary cutaneous melanomas referred to a major melanoma treatment center, the precision, reproducibility and completeness of external pathology reports and pathology reports generated by central review of each case. We also sought to determine whether the completeness and structure of pathology reports changed over the study period. Methods Details of external pathology reports and corresponding internal review reports were extracted from the melanoma research database of our pathology research center for 4924 primary cutaneous invasive melanomas diagnosed and treated between 2001 and 2011. Interobserver variation and the completeness of reports were assessed for the following 10 features: Breslow thickness, tumor mitotic rate, ulceration, Clark level of invasion, microsatellites, vascular invasion, lymphatic invasion, associated nevus, regression, and histologic subtype. Results Interobserver agreement was excellent for Breslow thickness (Intraclass Correlation Coefficient (ICC) 0.984), tumor mitotic rate (ICC 0.833) and ulceration (Kappa statistic 0.823). All three of these important pathological variables were included in 66.9% and 92.4% of external and internal pathology reports, respectively. There was a marked and significant improvement in the completeness of reports (particularly of external reports) for most pathologic features over the 10-year study period. Conclusions The essential staging criteria specified by the 2009 American Joint Committee on Cancer Staging System for cutaneous melanoma (tumor thickness, mitotic rate and ulceration) showed excellent reproducibility between external and internal pathologists. The quality of community-based pathology reporting on melanoma in New South Wales improved between 2001 and 2010.

P183

Behavior of Cutaneous Adnexal Neoplasms J. Wong,* C. Puleo, S. Iyengar, A. Chen, D. Almendares, K.J. Fisher, C.W. Cruse, A.A. Sarnaik, R.J. Gonzalez, J.L. Messina, V.K. Sondak, J.S. Zager. *Surgery, Moffitt Cancer Center, Tampa, FL.*

Introduction: Malignancies arising from cutaneous adnexae (eccrine and apocrine sweat glands, sebaceous glands and hair follicles) are clinically diverse. Given their rarity, the behavior, treatment and prognosis of these neoplasms remains unclear. Methods: A single institution database of patients (pts) treated for adnexal malignancies was retrospectively reviewed. Statistical analyses were performed with eccrine, sebaceous, and apocrine as distinct subgroups. Results: From 1998-2012, 71 pts were identified, 50 (70%) with eccrine histology (including porocarcinoma, microcystic adnexal carcinoma, and eccrine NOS), 10 (14%) sebaceous, 7 (10%) apocrine, 3 (4%) unspecified, and 1 (1%) pilar. Median age was 62 years. Lesions were located most commonly in the head/neck (49%), followed by extremity (27%), and trunk (23%). 65 (92%) underwent wide excision of the primary lesion. 15 (21%) underwent sentinel lymph node biopsy (SLNB); 4 (26%) had a positive SLNB (SLNB+) of whom 2 underwent completion lymphadenectomy (CLND). Seven (10%) presented with regional lymphadenopathy and underwent CLND (Table). In total, 11 pts developed recurrent disease; ten (10/50, 20%) with eccrine: 6 recurred locally, 3 regionally, and 1 with distant metastasis. One apocrine pt (1/7, 17%) recurred distantly. Of the 4 pts with microscopic lymph node disease (SLNB+), none recurred. In contrast, 3/7 (43%) pts with macroscopic regional nodal disease recurred: 2 regionally and 1 distantly (Table). All 3 pts received adjuvant therapy; the 2 regional recurrences followed CLND for head/neck lesions. Median overall survival (OS) was 97.6 months. There was no significant OS or disease-free survival (DFS) difference based on tumor location, histologic subtype, or SLNB status. A subgroup analysis performed on the eccrine group demonstrated no OS or DFS difference between porocarcinoma vs. other histologies. Conclusion: Adnexal eccrine malignancies, particularly porocarcinoma, frequently present with lymph node disease and have a higher likelihood of recurrence; however, no survival differences were noted based on subtype. SLNB may provide a disease-free advantage for these neoplasms, as pts with clinically evident lymphadenopathy tend to recur more frequently.

Histology				Recurrence		
	Positive SLNB	Presentation with regional nodal disease	Completion regional node dissection	Local	Regional	Distant
Apocrine (N=7)	1/1	2 (29%)	3 (43%)	0%	0%	1 (14%)
Sebaceous (N=10)	0/1	0%	0%	0%	0%	0%
Eccrine (N=50)						
Porocarcinoma (N=18)	0/1	5 (28%)	5 (28%)	3(17%)	3 (17%)	0%
Microcystic adnexal carcinoma (N=13)	1/2	0%	0%	1 (8%)	0%	0%
Eccrine NOS (N=19)	2/9	0%	1 (11%)	2 (11%)	0%	1 (5%)
Unspecified (N=3)	0/1	0%	0%	0%	0%	0%
Pilar (N=1)	0/0	0%	0%	0%	0%	0%

P184

Imatinib Modulates CD4+ T cells in Gastrointestinal Stromal Tumor (GIST) V.P. Balachandran,* M. Cavnar, S. Zeng, Z.M. Bamboat, L. Ocuin, H. Obaid, E. Sorenson, T. Kim, R. Popow, R.P. DeMatteo. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction Imatinib mesylate partially exerts its antitumor effects in GIST by inhibiting tumor production of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido), thereby activating antitumor CD8+ T cells. The role of conventional CD4+ T cells (CD4+FoxP3-) in imatinib therapy is unknown. We examined the effects of imatinib on CD4+ T cells in GIST. Methods We injected imatinib or saline intraperitoneally for one week to KitV558-/+ mice that develop spontaneous GISTs. 1-methyl-D-tryptophan (D-1MT), an Ido inhibitor was given via oral gavage. We assessed treatment response by tumor weight and immune cells by flow cytometry. Regulatory T cells (Treg) were defined as CD4+FoxP3+. Matched blood and tumor specimens from GIST patients were freshly analyzed for immune composition. Tumors were classified as untreated, sensitive, or resistant to imatinib based on radiologic assessment just before the time of surgery. Results Imatinib increased the number, activation, and degranulation of CD4+ T cells in the draining lymph node (DLN) but not the spleen of GIST mice ($p<0.05$). In the tumor, imatinib increased CD4+ T cell number, activation, proliferation, and the intratumoral CD4+/Treg ratio ($p<0.05$). Conversely, Ido inhibition did not alter CD4+ T cell number, activation, proliferation, or the CD4+/Treg ratio in the DLN or tumor. In untreated human GISTs (n=14), CD4+ T cells demonstrated greater activation and memory phenotype compared to autologous blood CD4+ T cells, but secreted Th2 cytokines on in vitro restimulation ($p<0.05$). Imatinib treatment altered the intratumoral CD4+/Treg ratio, with a higher ratio in sensitive tumors (n=17) compared to resistant tumors (n=12; $p<0.05$). Conclusion In mouse GIST, imatinib activates CD4+ T cells independently of Ido and increases the intratumoral CD4+/Treg ratio, a hallmark of immunologic outcome. Similarly, imatinib sensitive human GISTs have a higher CD4+/Treg ratio than resistant tumors. Hence, CD4+ T cells may contribute to the antitumor effects of imatinib in GIST. Combination immunotherapy with imatinib and CD4+ T cell modulating agents may be a promising therapy for GIST.

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Functional Analysis of Gene Profiling of Melanoma: Potential Significance of Over-Expression of the Cell-Cycle Regulatory Gene, ETV1 R. Essner,* K.W. Gong, B. Chmielowski, R. Finn, D. Slamon. *Oncology, UCLA, Santa Monica, CA.*

Introduction: Metastatic melanoma is largely refractory to existing therapies, the 5-year survival is < 5%, despite the development of several new therapies in the last year, including the oral BRAF inhibitor, Zelboraf. Better understanding of melanoma biology, especially the gene expression profile between primary and metastatic melanoma, may provide useful information for this disease. Methods: RNA was extracted from 89 melanoma tumors. The gene expression profile was investigated with microarray and was analyzed with MATLAB software. Results: 8261 differential expressed genes were identified between primary and metastatic melanoma at statistical level p <0.01 and false discovery rate (FDR) of 5%. 8261 differentially expressed genes were enriched with genes which were involved multiple signalling pathways. Primary melanoma microarrays were analyzed according to the thickness of tumor. Group A: the thickness of a tumor less than 2.0 mm, 20 microarrays. Group B: the thickness of a tumor was equal or more than 2.0 mm, 11 microarrays. 981 genes were identified as differentially expressed between Group A and Group B at statistical level p<0.01 and FDR=5%. 657 out of 981 differentially expressed genes were shared with original 8261 differentially expressed genes. We believed these 657 genes were related to malignant potential of melanoma. One of the genes identified in the analysis was the cell-cycle regulatory gene ETS. ETS variant gene 1(ETV1) gene expression was significantly (p<0.05) increased in melanoma metastases and primary melanoma with tumour thickness >2.0 mm. We found that ETV1 mRNA levels in BRAF inhibitor resistant cell lines were significantly (p<0.05) higher than that in BRAF inhibitor sensitive cell lines (expression ratio: 0.927±0.6 vs. 0.230±0.057, p<0.0001) and the parental cell lines. Conclusion: The significance of up-regulated ETV1 gene expression in high risk primary and metastatic melanoma, specifically BRAF inhibitor resistant cell lines, may lead to a better understanding as to BRAF inhibitor resistance seen clinically in metastatic melanoma and development of new therapies for these patients.

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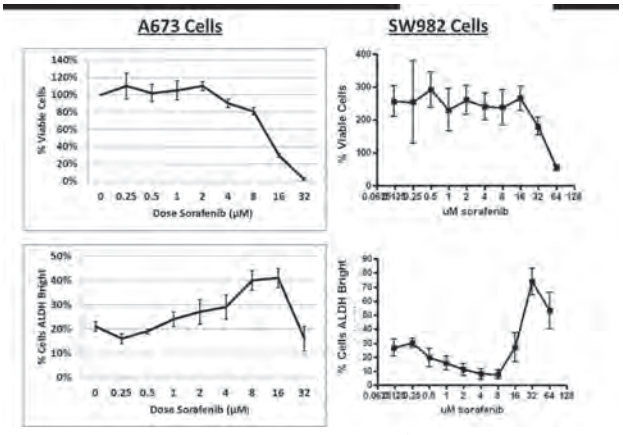
Sorafenib Enriches for Sarcoma Cancer Stem Cells *In Vitro* R.J. Can-ter,* E. Ames, J. Tellez, R.C. Smith, J. Perez, A.M. Monjazeb, W.J. Murphy. *Surgery/Surgical Oncology, UC Davis Medical Center, Sacramento, CA.*

Background: Cancer stem cells (CSCs) are a putative source of relapse in many cancers following anti-proliferative therapies. We hypothesized that tyrosine kinase inhibition (TKI) and radiotherapy (RT) would enrich for CSCs in sarcoma cell lines. Methods: A673 Ewing's sarcoma and SW982 synovial sarcoma cells were exposed to sorafenib and RT in a dose- and time-dependent fashion. Cultured cells were harvested and stained with fluorochrome-conjugated antibodies against human CSC markers including CD133, CD24, CD44, and aldehyde dehydrogenase (ALDH). Cell viability was analyzed using 7-Aminoactinomycin (7-AAD). Data were acquired using a BD Fortessa cell sorter (BD Biosciences) and analyzed with FlowJo software version 7.2. Parametric and non-parametric statistical tests were performed as appropriate. Results: Short-term exposure (≤1 day) to sorafenib demonstrated a linear dose-dependent cytotoxicity for A673 cells at doses ≥ 4 μM, while SW982 cells required doses ≥ 16 μM. At 24 hours, A673 cell viability decreased from 100% at 1 μM sorafenib to 0% at 32 μM (P<0.05). By day 5, A673 cells exposed to sorafenib doses < 32 μM recovered log-phase growth, while cells exposed to doses > 32 μM remained non-viable. Baseline CSC phenotyping of A673 cells demonstrated 55±5% CD133+, 12±7% ALDH+, 14% CD44+, and 0% CD24+ sub-populations. Baseline CSC phenotyping of SW982 cells demonstrated 0.2±0.9% CD133+, 42±8% ALDH+, 95±5% CD44+, and 40±7% CD24+. A673 cells exposed to 24h sorafenib increased the ALDH+ fraction to 40±3% (> 3-fold increase) at sorafenib 16 μM (P<0.05). SW982 cells showed a non-significant increase in the ALDH+ fraction at doses ≤ 16 μM. Although single fractions of RT were anti-proliferative to A673 cells starting at doses ≥5 Gy, there was not an additive effect of 2.5 Gy RT with sorafenib on cell viability or CSC marker expression. Conclusion: Sorafenib exerts an anti-proliferative effect on sarcoma cells but enriches for sarcoma CSC. The magnitude of these effects appears to be inversely correlated to baseline ALDH+ levels. Sustained anti-sarcoma therapeutic effects may require targeting of the CSC population following anti-proliferative therapy.



In vitro response of sarcoma cell lines to Sorafenib demonstrates increasing cytotoxicity with increasing doses (top panels), while simultaneously enriching for the ALDH+ sub-population (bottom panels).

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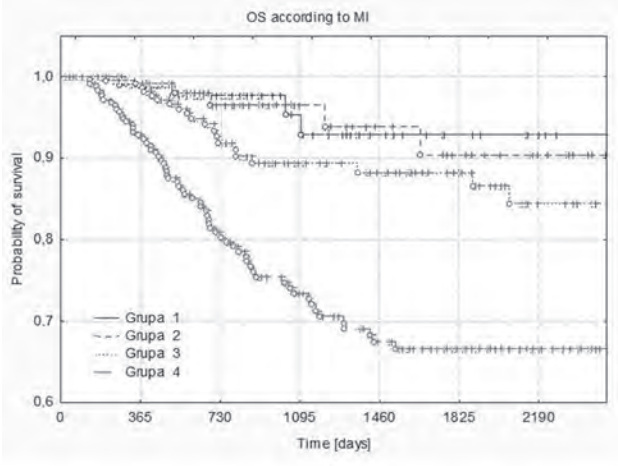
The Significance of Mitotic Index in Cutaneous Melanoma Patients Undergoing Sentinel Node Biopsy P. Rutkowski,[1] K. Szydlowski,[2] H. Kosela,[1]* E. Bakula-Zalewska,[3] W. Michej,[3] M. Zdzienicki,[1] A. Gluszcz,[1] T. Switaj,[1] A. Van Akkooi,[4] Z. Nowecki.[1] *1. Department of Soft Tissue/Bone Sarcoma and Melanoma Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; 2. Department of Surgical Oncology; Regional Hospital Elblag,, Elblag, Poland; 3. Departament of Pathology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; 4. Erasmus University Medical Centre – Daniel den Hoed Cancer Centre,, Rotterdam, Netherlands.*

The aim of the study was analysis of the relevance of mitotic index (MI) of primary tumor in patients undergoing sentinel node biopsy (SLNB). Methods: 805 patients with known MI underwent SLNB between 2000 and 2010. Median Breslow thickness was 2.4 mm, 44% of cases were ulcerated. Metastases to SLNs were detected in 23%. Median follow-up time was 36 months. Results: The distribution of MI in primary tumors was as follows: 123 cases (15.3%) had MI <1/mm2 (group 1), 142 cases (17.6%) – MI=1/mm2 (group 2), 262 cases (32.6%) - MI >1-5/mm2(group 3),278 cases (34.5%) – MI >5/mm2 (group 4). MI correlated with metastases to SLNs [18 SLNs+ (15%) cases with MI<1/mm2; 21 SLNs+ (15%) cases with MI=1/mm2, 62 SLNs+ (24%) cases with MI >1-5/mm2; and 83 SLNs+ (30%) cases with MI >5/mm2 (p<0.001)]. In pT1 tumors: we have found any metastases to SLNs in cases with MI <1/mm2 (0/39), for 46 tumors with MI 1/mm2 we detected 4 SLNs+ (10.8%). Similarly, in pT2 tumors: positive SLNs were detected in 4 of 47 tumors with MI <1/mm2 (8.5%), 6 of 53 tumors with MI=1/mm2 (11.3%), 8 of 75 tumors with MI >1-5/mm2 (10.7%), and 7 of 44 with MI>5/mm2 (16%). MI correlated with patients overall survival (OS), 5-years OS rates according to MI were: 92% for MI<1/mm2, 90% for MI=1/mm2, 87% for MI <1-5/mm2, 65% for MI>5/mm2 (p<0.0001). In multivariate analysis the significant factors for OS were: presence of metastases to SLN, primary tumor Breslow thickness and MI. Conclusions: We have confirmed the prognostic relevance of MI for primary melanomas undergoing SLNB. For primary melanomas with Breslow thickness ≤1.0 mm the SLNB should be considered if MI is ≥1/mm2. MI correlated with presence of metastases to SLNs and patients outcomes.



P188

Advanced Imaging for the Detection of Occult Metastatic Disease in Patients with American Joint Committee on Cancer Stage III Melanoma H. Beitollahi,* K. Jaap, M. Hunsinger, N. Woll, M. Shabahang, J. Blansfield. *General Surgery, Geisinger Medical Center, Danville, PA.*

Background: Melanoma patients with nodal metastases (American Joint Committee on Cancer (AJCC) stage III) are at significant risk for recurrence and distant disease. National Comprehensive Cancer Network guidelines recommend consideration of baseline imaging with computed tomography (CT), positron emission tomography (PET)/CT or magnetic resonance imaging (MRI); however, the data supporting this recommendation is limited. This study evaluates the utility of PET/CT and dedicated brain imaging for staging in stage III melanoma. Methods: This is a retrospective review of patients with AJCC stage III melanoma treated at a single institution between 2001-2012. Patients without clinical evidence of distant disease underwent staging workup within one month of diagnosis, including PET/CT with or without brain imaging. False positive (FP) rates and positive predictive values (PPV) of diagnostic imaging were analyzed. Results: Eighty-eight patients had stage III melanoma. The average Breslow thickness was 3.22 mm; 33 patients (37.5%) had ulcerated lesions. Twelve patients (13.6%) had palpable nodes at diagnosis. Seventy-two patients (81.8%) underwent PET/CT as part of the staging work up. Twenty-three studies (31.9%) had positive findings. Ten patients had positive findings on the CT portion, five had positive findings on the PET portion and eight had positive findings that correlated on PET and CT. Two patients had true positive findings and 21 patients had FP findings, yielding a FP rate of 30% and a PPV of 8.7%. Twenty patients (87%) had additional imaging performed due to the positive findings. Twenty-two patients (25%) underwent imaging specifically to evaluate for brain metastases. Seven patients (31.8%) underwent CT of the brain and 15 (68%) underwent brain MRI. There was one positive result in the brain MRI group (6.6%); this was a FP result. Conclusion: There are a high number of false positive results when diagnostic imaging is used as a routine component of the staging workup for asymptomatic patients with stage III melanoma. The use of routine PET/CT and dedicated brain imaging in these patients may not be warranted.

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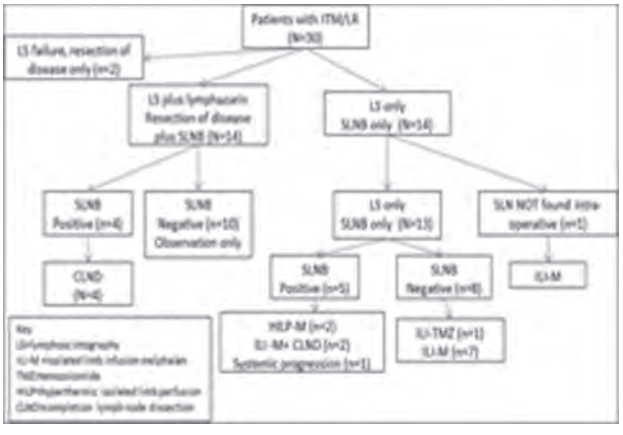
Sentinel Lymph Node Biopsy to Guide Management in Patients with Locally Recurrent Melanoma G. Beasley,* P. Speicher, K. Sharma, B. Jiang, M. Lidsky, K. Bronson, P. Mosca, D.S. Tyler. *Duke university, Durham, NC.*

Background: Even after negative sentinel lymph node biopsy (SLNB) for primary melanoma, patients who develop in-transit melanoma (ITM) or local recurrences (LR) may have subclinical regional lymph node involvement not detected by physical exam or radiographic imaging. Methods: A prospective database identified 30 patients with ITM/LR who underwent Tc-99m sulfur colloid lymphoscintography alone (n=14) or in conjunction with lymphazurin dye (n=16) administered only if the ITM/LR was excised. For patients with multiple lesions, mapping was performed by injecting the most proximal lesion. Results: Four patients had previously undergone wide local excision (WLE) plus SLNB with completion lymph node dissection (CLN) for their primary melanoma, 16 patients had undergone WLE plus SLNB of their primary melanoma, 7 patients had undergone WLE only and 3 patients had ITM of unknown primary. Lymphoscintography at time of presentation with ITM/LR was successful in 93% (28/30) cases, and at least one SLN was found intraoperatively in 96% (27/28) cases. The SLNB was positive in 33% (9/27) cases. CLN was performed in 89% (8/9) of cases including 4 patients with unresectable ITM who also underwent regional chemotherapy treatments. Eight patients with negative SLNB and unresected ITM underwent regional chemotherapy only as outlined in Figure 1. Conclusion: Here we refine a methodology for mapping multifocal ITM and suggest a 33% rate of SLN positivity in patients presenting with ITM or LR. Performing SLNB can optimize local, regional, and systemic treatment strategies for patients with locally recurrent or in-transit melanoma.



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Vital Blue Dye Use in Sentinel Lymph Node Biopsy for Melanoma Compared with Radioisotope Alone T.S. Ellison, A.M. Winder, V. Erath, M. Hunsinger, N. Woll, M. Shabahang, J.A. Blansfield.* *Surgical Oncology, Geisinger Medical Center, Danville, PA.*

Background: Sentinel lymph node biopsy (SLNB) for melanoma has become the standard for staging but the best method of locating the sentinel node remains unclear. Specifically, both blue dye (BD) and radioisotope (RDI) are used to locate the sentinel node but there is no clear indication that BD in addition to RDI is beneficial and there is evidence to suggest BD can be harmful. The use of blue dye can lead to anaphylactic reactions, skin tattooing, plus the additional cost and time of injection. The aim of this study was to evaluate whether BD improved the yield of SLNB compared with RDI alone in patients with melanoma. Methods: This is a retrospective cohort study of 332 patients who had SLNB for melanoma from 2005 to 2012 at a single institution. Two hundred sixty-four patients underwent SLNB with BD in addition to RDI and 68 patients underwent SLNB with RDI alone. The primary outcomes measured in this study were overall survival time, false negative rate, and number of lymph nodes resected in each group. Results: Baseline demographics in each group were similar with the exception of Breslow thickness. Breslow thickness was higher in the RDI group compared to the combined group (1.8 vs. 1.25mm, $p<0.0050$). The average number of lymph nodes removed was the same for each group (2 nodes). The RDI group had a higher rate of positive sentinel nodes (28% vs. 24%) but this was not statistically significant. The overall survival was not statistically different between groups ($p=0.1935$). False negative rates were low for both groups and there was not a statistically significant difference between groups. The false negative rate was 1.47% for the RDI group and 1.14% for the RDI/BD group ($p=0.99$). Conclusions: The addition of BD did not lead to a higher detection rate of sentinel lymph nodes in patients with melanoma. There was no decrease in false negative rates when BD was used in addition to RDI and most importantly there is no increase in survival in patients who had BD in addition to RDI for their SLNB. This study suggests BD does not add to RDI for SLNB in patients with melanoma and its use should be seriously questioned.

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Electrochemotherapy for Treatment of Locally Advanced Superficial Cancer: Results from a Single Institution E. Pennacchioli,* A. Intelisano, F. Verrecchia, G. Tosti, E. Cocorocchio, G. Spadola, P. Ferrucci, A. Testori. *Melanoma and Sarcoma Surgery, European Institute of Oncology, Milan, Italy.*

Introduction: ECT has been widely used for the treatment of superficial localization of different cutaneous and non-cutaneous diseases. We analyse the outcome of this treatment in relation to different histotypes and the length of response. Methods: From May 2006 to August 2011, 179 ECT treatments in 108 evaluable patients at IEO, Milan. Median age was 70 years. Of patients treated for primary disease (62 pts), 40% (25) are Squamous cell carcinoma, 37% (23) are Basal cell carcinoma and 8% (5) are melanoma. 65% of patients had at least 2 treatments, 13% more than 3 treatments. In the group of patients treated for metastatic disease 76% (89/117) are melanoma. Bleomycin was administered iv in 159 cases (89%) and intratumoral in 20 cases (11%). For post-operative monitoring of response a recorded clinical evaluation was done in all patient at day 30, 60, 90, 180, 360. The evaluation of response was recorded as follow: CR for radical eradication (100%); PR for partial eradication (between 1 and 99%); NR for no response; PRO for progression of disease, both for increase of pre-existing nodules or in the event of new nodules. Results: One month after treatment were recorded as follows: CR 12% of cases, PR in 84%; NR in 4%; 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). By histotype, CR was obtained in 57% cases of Kaposi 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 on survival was not evaluated, as ECT is a local treatment. Local toxicity consist in mild pain, self-retaining serum effusion for a couple of weeks and rare ulceration of treated nodules. 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 and BCC). The length of response should be used in order to associate a systemic treatment, possibly an immunotherapy.

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Predictors of Patient Response to Isolated Limb Perfusion for Metastatic Melanoma C.M. Webb,* H. Wachtel, E.K. Bartlett, L.C. Lowenfeld, R.R. Kelz, G.C. Karakousis, D.L. Fraker. *Hospital of the University of Pennsylvania, Philadelphia, PA.*

Introduction: The published complete response (CR) rate for isolated limb infusion is 20-30%. The CR rate for isolated limb perfusion (ILP) is 50-60%, however factors predictive of response are poorly characterized. We examined our large single surgeon series of patients undergoing ILP to determine factors associated with CR with particular attention to perfusate pH. Methods: Between 2004-2012, 79 consecutive patients underwent hyperthermic ILP with melphalan for in-transit melanoma. Retrospective chart review was performed and patients with ≥60 days follow-up (n=55) were included in analysis. Variables examined included patient age, gender, location of primary melanoma (upper versus lower extremity), maximal pH of the ILP perfusate, presence of lymph node metastasis, and number of in-transit metastases. Primary outcome measure was CR rate. Student's T test or Fisher's exact test were performed as appropriate; a p-value of ≤0.05 was considered significant. Results: Of the 55 patients analyzed, 27 (49%) had a CR after ILP, consistent with previous reports. Patients with CR were not significantly different from those without CR with respect to age, gender, location of primary melanoma, or presence of lymph node metastases. Patients with increasing numbers of in-transit metastases were less likely to demonstrate CR (p=0.02). CR patients were more likely to have a lower perfusate pH (p=0.04). Patients with a consistently acidic pH (≤7.40) had a 60% CR rate, while patients with a maximal pH in the alkalotic range had a 30% CR rate (p=0.05). Extremely acidic pH (≤7.25), however, was not associated with an increase in CR rate when compared to moderately (7.26-7.4) acidic pH (47% versus 70%). Conclusions: Number of in-transit metastases and perfusate pH were significantly correlated with CR in patients undergoing ILP for melanoma. While moderately acidic pH is associated with improved CR rates, extremely acidic pH does not appear to further improve CR, but may contribute to morbidity. Maintaining an acidic perfusate may significantly improve CR rates for patients undergoing hyperthermic ILP with melphalan.

Table I: Pre- and post-operative findings in patients with metastatic melanoma undergoing isolated limb perfusion

	Total population (55)	No/partial Response (28)	Complete Response (27)	P-value
Gender				
Female (%)	33 (60)	14 (50)	19 (70)	0.17
Male (%)	22 (40)	14 (50)	8 (30)	0.17
Age (years)				
Mean (SD)	66 (12.9)	67.1 (14.4)	64.9 (11.3)	0.54
Location				
Upper extremity	6 (11)	4 (14)	2 (7)	0.67
Lower extremity	49 (89)	24 (86)	25 (93)	0.67
pH ILP perfusate				
≤7.25	15 (27)	8 (29)	7 (26)	0.04
7.26-7.40	20 (36)	6 (21)	14 (52)	
≥7.41	20 (36)	14 (50)	6 (22)	
LN metastases				
Present (%)	37 (67)	18 (64)	14 (52)	0.42
In-transit metastases				
<5 (%)	14 (25)	6 (21)	8 (30)	0.02
6-15 (%)	11 (20)	2 (7)	9 (33)	
>15(%)	30 (55)	20 (71)	10 (37)	

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Combined Radio- and Fluorescence-guided Sentinel Node Biopsy in Melanoma Patients using a Hybrid Tracer O.R. Brouwer,[1]* B. Schaafsma,[2] N. Van den Berg,[2] M.C. Klop,[1] A. Balm,[1] O.E. Nieweg,[1] A. Vahrmeijer,[2] F. Van Leeuwen,[2] R. Valdés Olmos.[1] *1. Nuclear Medicine, Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, Netherlands; 2. Leiden University Medical Center, Leiden, Netherlands.*

INTRODUCTION Indocyanine green (ICG)-99mTc-nanocolloid is a novel hybrid tracer for sentinel node (SN) biopsy. 99mTc allows for preoperative lymphoscintigraphy, SPECT/CT and intraoperative tracing of hot nodes with a gamma ray detection probe, while ICG enables intraoperative visualization of lymph vessels and sentinel nodes using near-infrared fluorescence imaging. The present study aims to explore the SN identification rate of this novel versatile tracer in a large population of melanoma patients. METHODS Ninety-six patients with melanoma of the head and neck (n=46), trunk (n=35) or extremities (n=15) were studied. Conventional lymphoscintigraphy with subsequent SPECT/CT was performed after intradermal administration of ICG-99mTc-nanocolloid. The operation was performed immediately following SPECT/CT imaging or the next day. Patent blue dye was used in all patients, except the ones with a melanoma in the face. Intraoperatively, SNs were pursued using the vital dye and the probe, followed by optical verification with a near-infrared handheld camera. A portable gamma camera was used to confirm complete removal of all SNs. RESULTS Preoperative imaging revealed at least one SN in all 96 patients (total: 222 SNs). Intraoperatively, 266 SNs were harvested. Five percent of the harvested SNs were located near the injection site and were localized by the fluorescence camera. The other SNs were harvested using a combination of vital blue dye, radioguidance and fluorescence imaging. Ex vivo, all SNs were both radioactive and fluorescent, whereas in the 70 patients in whom blue dye was used, only 113 of the 190 SNs had stained blue (59%). Nineteen patients had a tumor-positive SN (20%). CONCLUSION The hybrid tracer ICG-99mTc-nanocolloid enabled preoperative imaging and intraoperative radio- plus fluorescence-guided SN biopsy in all 96 patients. The hybrid tracer was found to be particularly useful for the detection of SNs in the neck, and for sentinel nodes that failed to accumulate patent blue dye. A randomized study comparing the new radiopharmaceutical to the standard agent appears appropriate.

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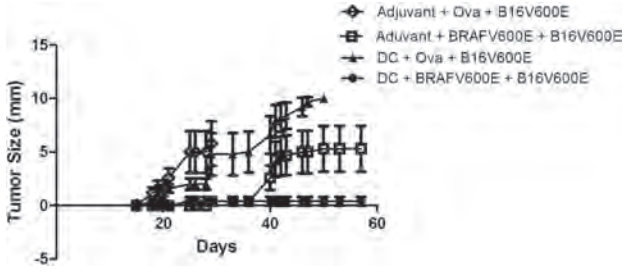
Type I Polarized Dendritic Cell-based Vaccine Effectively Targets BRAFV600E in Melanoma J. Cintolo,[1]* R. Somasundaram,[2] S. Xu,[1] M. Gupta,[1] B.J. Czerniecki.[1] *1. Harrison Department of Surgical Research, Hospital of the University of Pennsylvania, Philadelphia, PA; 2. Wistar Institute, Philadelphia, PA.*

Introduction: Dendritic cell (DC)-based vaccines may be superior immunogens and are being investigated to treat a variety of cancers. We tested the ability of type I polarized DC (DC1) pulsed with BRAF V600E to elicit antigen-specific T cell responses and prevent melanoma formation in a mouse model. Methods: Bone marrow precursors were matured to a DC1 phenotype. Maturation was confirmed by detection of cell surface markers using flow

cytometry. Secretion of IL-12p70 was measured by ELISA. Cohorts of 10 C57BL/6 mice received 3 intradermal vaccinations at 2 week intervals of DC1s pulsed with either Ova peptide or affinity modified BRAF peptide. Two additional cohorts were vaccinated using Freund's adjuvant combined with the same peptides. One week following vaccination, mice were challenged with B16 tumor cells expressing V600E mutation (B16V600E+) or B16 cells expressing Wt epitope (B16Wt). Antigen specific CD8+ responses were assessed from spleen cells by IFN-γ ELISPOT and differences were determined by two tailed t test. Group survival was compared with the log rank test; differences in tumor growth over time were compared using t-tests. Results: DC1s expressed CD80, CD86, and CD83 and demonstrated a 10,000fold increase in IL-12 secretion compared to immature DCs suggesting a mature phenotype. CD8+ cells isolated from mice vaccinated with BRAF peptide demonstrated increased antigen specific IFN-γ secreting cells compared with control peptide (p=0.02). Mice vaccinated with DC1s-pulsed with mutated BRAF peptide when challenged with B16V600E+ demonstrated improved survival and lower cumulative tumor burden over time compared to control mice vaccinated with the ova peptide. Mice vaccinated with BRAF–pulsed DC1s had less tumor burden compared with those vaccinated using adjuvant and BRAF peptide (p=0.001). Only 20% of DC1 vaccinated mice developed tumors compared with 80% in the adjuvant group. Conclusions: Vaccinating mice with BRAF pulsed-DC1s elicited antigen-specific CD8+ T cells and protected mice challenged with B16V600E+ melanoma superior to combinations of Freund's adjuvant and peptide suggesting BRAF pulsed-DC1 should be explored in melanoma treatment models.



Tumor growth over time after challenge with B16V600E

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Positron Emission Tomography (PET) for Staging of Cutaneous Melanoma in the United States: A Population-Based Analysis

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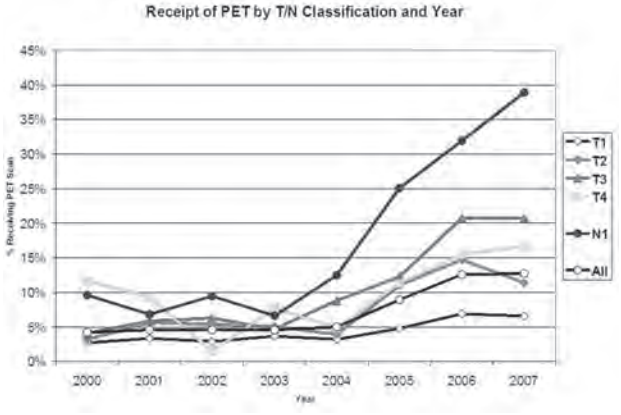
Introduction Routine imaging with whole body PET for the staging of cutaneous melanoma is not supported by current evidence. We sought to investigate the use of whole body PET in the staging of cutaneous melanoma in the United States. Methods Patients with newly diagnosed cutaneous melanoma between 2000-2007 were identified from the Surveillance Epidemiology End Results-Medicare registry. Any PET scan performed within 90 days following diagnosis was considered a staging PET scan. Patients with metastatic disease were excluded. Trends in the use of PET were studied and multivariate analysis used to identify predictors of use. Results A total of 26,300 patients were identified, of which 1,968 (7.5%) underwent staging with a PET scan. The mean age was 76.1 years and the majority (61.7%) were male. Breakdown by T classification was as follows: T1 (61%), T2 (16%), T3 (12%), and T4 (11%). Positive regional nodes were present in 3,646 (13.9%) of patients. The use of PET for staging increased from 4.5% in 2000 to 12.8% in 2007 overall. When stratified by T classification, PET scanning was used for 4.9% of T1, 8.8% of T2, 12.2% of T3 and 15.0% of T4 tumors; of patients with node-positive disease, 16.3% had a PET scan. The use of PET increased significantly over the period of our study for patients with all T classifications and node positive patients (Figure). On multivariate analysis, patients with more advanced T classifications (OR 2.35 for T4 vs. T1, 95% CI 1.97-2.81), node positivity (OR 5.08 vs. node negative, 95% CI 4.50-5.73) and more recent diagnosis were more likely to undergo PET scans. Conversely, patients >85 years old (OR 0.62 vs. age 65-75, 95% CI 0.53-0.73) and patients in larger metropolitan areas (OR 0.88, 95% CI 0.79-0.98) were less likely to receive PET scans. Conclusions Overall, the use of whole body PET for staging of cutaneous melanoma is low. However, temporal trends show a sharp escalation in use which is contrary to current guidelines. Further research is needed to identify factors driving this increase.



Figure

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High Mitotic Rates in Patients with Cutaneous Melanoma

V.H. Barnica,[1]* S.S. Reddy,[2] H. Wu,[3] F. Zhu,[4] A.J. Olszanski,[5] J.M. Farma.[6] *1. Fox chase cancer center, Philadelphia, PA; 2. foxchase cancer center, Philadelphia, PA; 3. foxchase cancer center, Philadelphia, PA; 4. foxchase cancer center, Philadelphia, PA; 5. foxchase cancer center, Philadelphia, PA; 6. Foxchase cancer center, Philadelphia, PA.*

OBJECTIVES: High mitotic rate is a poor prognostic variable in patients with cutaneous melanoma. The aim of our study was to determine the impact and outcomes in melanomas patients with high mitotic rates >8/mm2. METHODS: A retrospective review of our database of melanoma patients was performed from 2008 to 2012. We examined age, sentinel lymph node(SLN) status, recurrence and survival in patients with high mitotic rates, defined as ≥ 8mm2. Patients were stratified into 3 groups based on mitotic rate; zero, low(1-7/mm2) and high(≥8/mm2) and evaluated related to stage and outcomes. Low (1-7/mm2) and high((≥8/mm2)mitotic rate cut off was determined by recurrence free survival. RESULTS: Of 239 patients [median age 61.4 years(range: 23-98)], 33(13.8%) patients presented with a high mitotic rate ≥8/mm2(range 8-47/mm2). In patients with high mitotic rate, tumor location was head/neck (n=5), extremity (n=9) and trunk (n=19). Median tumor thickness was 3.35mm(0.68-21mm) and 25(76%) were ulcerated. SLN biopsy was performed in 28(85%) of patients and was positive in 10(30%) patients. Completion lymphadenectomy was performed in 6(18%) patients with positive SLN. In patients with high mitotic rate recurrence occurred in 9(27%) patients, 1 locally and 9 distant. Sites of distant recurrence were M1a(n=2), M1b(n=4), and M1c(n=3). Median disease free survival(DFS) was 9 months and median overall survival(OS) was 13 months. When all 239 patients were stratified to zero, low or high mitoses we found no correlation between mitotic rate and age(p=0.17). As expected higher T-stage and overall stage correlated with higher mitotic rates($p<0.0001$) and SLN positivity ($p<0.01$). Overall DFS was worse with higher mitotic rates($P<0.006$). The unadjusted hazard ratios were 3.56(low mitoses)[95%CI 0.44-28.6] and 13.2(high mitoses)[95%CI 1.67-103.8] when compared to zero mitoses. CONCLUSIONS: In our study high mitotic rate(>8/mm2) confers a poor prognosis with a 30% chance of SLN positivity and 27% of recurrence and an OS of 13 months. Further studies are warranted to evaluate more aggressive adjuvant treatment in aims to decrease the chance of local and distant recurrence in this high-risk subset of melanoma patients.

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The Influence of Competing Causes of Mortality on the Natural History of Patients with Desmoplastic Melanoma D. Han,* G. Han, X. Zhao, N.G. Rao, J.L. Messina, A.A. Sarnaik, C.W. Cruse, R.J. Gonzalez, V.K. Sondak, J.S. Zager. *Moffitt Cancer Center, Tampa, FL.*

Introduction: The clinical course of patients with desmoplastic melanoma (DM) and the characteristics, particularly nodal status, that predict survival are not well reported. DM typically affects older patients who often have other comorbidities that can adversely affect survival. We sought to identify melanoma specific factors that influence survival in this population. Methods: Retrospective review from 1993 to 2011 identified 316 patients with primary DM. Clinicopathologic characteristics were reviewed and correlated with outcome. Results: Median age was 68.3 years and 72.2% of patients were male. Overall, 55 of 316 (17.4%) patients had nodal disease: 33 had a positive sentinel lymph node biopsy (SLNB) and 22 developed a nodal recurrence and either did not have a SLNB or had a false-negative SLNB. Node positive patients were younger (median age: 63 vs. 69 years) and had a higher rate of a mixed subtype compared with node negative patients (61.5% vs. 42.9%) with multiple logistic regression analysis showing that both of these factors significantly predicted nodal status ($p<0.05$). After a median follow-up of 5.3 years, recurrence developed in 87 (27.5%) patients, and a total of 111 (35.1%) deaths occurred of which only 47 (14.9%) deaths were melanoma-related. Multiple logistic regression analysis showed that age, Breslow depth, perineural invasion and margin status significantly predicted recurrence-free survival ($p<0.05$) while age, gender, Breslow depth and margin status significantly predicted overall survival ($p<0.05$). When melanoma-related deaths were considered, multiple logistic regression analysis showed that Breslow depth, tumor mitotic rate $\geq 1/mm^2$ and presence of nodal disease significantly predicted melanoma-specific survival (MSS, $p<0.05$). Conclusions: Similar to what is seen for conventional melanoma, nodal status is predictive of MSS in patients with DM. However, in the older population affected by this melanoma variant, a significant portion of deaths are not directly melanoma-related. Comorbidities, including surgical-related issues, should be considered in making staging and treatment decisions in these patients.

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Metformin and Polyamine Synthesis Inhibitor Exert Anti-Proliferative Effect on Melanoma *In Vivo* E.C. Hsueh,* Y. Zhang, G. Peng. *Saint Louis University, St. Louis, MO.*

We previously reported combination of Metformin and DFMO, an ornithine decarboxylase inhibitor, had significant activity against melanoma cell proliferation and migration in vitro. To explore the translational utility of this combination therapy, we determined the in vivo effect of this regimen in mouse melanoma models. Human melanoma cells SK-23 was injected SQ in BALB/c nu mice. Mouse melanoma cells B16 were used in C57BL/6 mice. After tumor nodule was established, mice were randomized to 4 groups of 6 : group 1 - IP injections of vehicle and normal drinking water, group 2 - 2% (w/v) DFMO in drinking water; group 3 - IP metformin (250 mg/kg/day), group 4 - DFMO plus metformin. Mice body weight and tumor volume were measured every 3 days. Tumor weight was measured on Day 20 at necropsy. Expression of AMP kinase, mTOR, p70S6K and 4E-BP1,Raf-1 and Raf-B was determined by Western blot. For comparison between groups, the student's t test was used and $p< 0.05$ was considered to be statically significant. No significant difference in body weight was observed among the mice in the 4 study groups during the study period. Both DFMO and metformin alone have significant in vivo anti-proliferative effect on human melanoma cell and mouse melanoma cell compared with control. However, the anti-proliferative effect of the combination treatment was significantly better than either regimen alone ($p< 0.001$) in both SK-23 model and B16 model. Average SK-23 tumor weight was 100 mg for control group compared with 45 mg for group 2 ($p<0.05$), 35mg for group 3 ($p< 0.05$), and 25mg for the combination group ($p< 0.001$). The combination treatment significantly enhanced AMPK activation and increased phosphorylation of AMPKα compared with metformin alone ($p<0.01$). The combination treatment resulted in inhibition of mTOR signaling with decreased phosphorylation of p70S6K and 4E-BP1 in treated cancer cells, when compared with individual drug treatments. Metformin and polyamine synthesis inhibition can significantly inhibit melanoma tumor growth in vivo. The mechanism of this inhibition is partly due to enhanced inhibition of mTOR signaling pathway.

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Limitations of Lymph Node Ratio and the Importance of an Adequate Lymph Node Dissection in Melanoma T.E. Grotz,[1]* M. Huebner,[1] B.A. Pockaj,[2] J.W. Jakub.[1] *1. Department of Surgery, Mayo Clinic, Rochester, MN; 2. Mayo Clinic, Scottsdale, AZ.*

Background: Lymph node (LN) metastases are an important prognostic factor in cutaneous melanoma. The AJCC 7th edition stratifies the heterogeneous prognosis of stage III melanoma by absolute number of LNs involved. However, given the variability of LN retrieval counts we hypothesize that lymph node ratio (LNR) may be a better prognostic factor. Methods: Retrospective cohort study of 411 stage III melanoma patients divided into two groups based on LNR (< 0.15, $n = 291$ and ≥ 0.15, $n = 120$). Completeness of LN dissection was estimated from the probability of understaging using Bayesian computation. Cox proportional hazard regression was used for univariate and multivariate analysis. Results: A median of 13 inguinal, 23 axillary and 31 cervical LNs were pathologically examined. LN characteristics such as N-stage (HR 2.13, $p < 0.0001$), extranodal extension (HR 1.92, $p = 0.002$) macrometastasis (HR 1.70, $p = 0.005$), non-SLN involvement (HR 1.65, $p = 0.005$), adequate LN dissection (HR 1.51, $p = 0.03$) and LNR (HR 1.46, $p = 0.03$) were significantly associated with melanoma-specific survival (MSS) on multivariate analysis. However, of all the nodal factors, only adequate LN dissection was able to further stratify any N-stage. Patients with N1 disease who had > 9 inguinal, > 16 axillary or > 21 cervical LNs removed had an improved 5-year MSS (74% vs. 68%, $p = 0.04$) compared to those with inadequate LN dissections (Figure 1B). N1 patients who had inadequate LN dissections had survival similar to N2 patients (65% 5-year MSS).This improvement in MSS is likely attributed to the minimized risk of understaging and not leaving behind untreated nodal micrometastatic disease (Figure 1A). Conclusion: LNR is an important prognostic factor in stage III melanoma following LN dissection; however, it was not independent of N stage and failed to further stratify any N-stage. N1 disease was able to be stratified by the completeness of LN dissection. Our results suggest N1 patients with LN counts below these minimum LN retrieval thresholds (9 inguinal, 16 axillary or 21 cervical) have an increased probability of understaging resulting in a prognosis similar to patients with N2 disease.

Figure 1A: Probability of missing one positive LN by number of LN examined

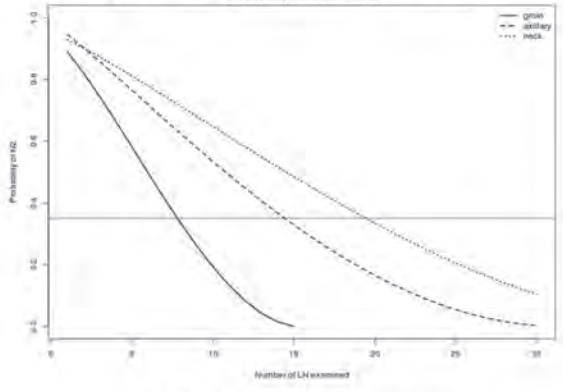
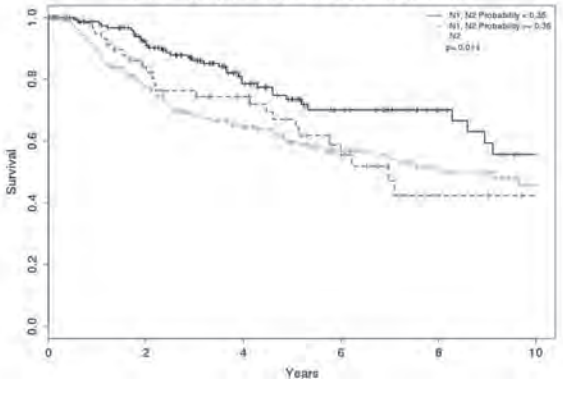


Figure 1B: Kaplan Meier estimate of melanoma-specific survival according to the probability of understaging given one positive LN



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Survival and Recurrence in Clinical Stage III Melanoma Patients with Whole Body FDG-PET and CT Added to the Diagnostic Work-up

M. Niebling,[1]* E. Bastiaannet,[2] O. Hoekstra,[3] H. Bonenkamp,[4] R. Koelemij,[5] H.J. Hoekstra.[1] *1. Surgery, University Medical Centre Groningen, Groningen, Netherlands; 2. Leiden University Medical Hospital, Leiden, Netherlands; 3. VU University Medical Centre Amsterdam, Amsterdam, Netherlands; 4. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 5. St. Antonius Hospital Nieuwegein, Nijmegen, Netherlands.*

Introduction The majority of melanoma patients present with stage I or II disease; however recurrences in the regional lymph nodes occur often. Whole-body FDG-PET and CT can be a valuable tool in staging these patients. The aim of this study is to analyze survival of FDG-PET and CT negative or positive melanoma patients and to assess which factors are associated with survival. Methods Patients with palpable and histologically or cytologically proven lymph node metastases of melanoma, referred to participating hospitals for examination with FDG-PET and CT were included in this study. Melanoma Specific Survival (MSS) and Disease Free Period (DFP) were analyzed for FDG-PET and CT positive and negative patients. Cox-regression analysis was performed to analyze which patient or melanoma characteristics were associated with MSS or DFP. Results For all patients 5 year MSS was 38.2% (95%CI: 32.2%-44.2%). For FDG-PET and CT negative and positive melanoma patients 5-year MSS was 47.6% (95%CI: 39.6%-55.6%) and 16.9% (95%CI: 6.9%-26.9%), respectively. Males; a positive FDG-PET and CT; and presence of extra nodal growth showed to be independent factors for worse MSS. Lymph nodes metastases (LNMs) in axilla compared to head or neck had significantly worse MSS (P=0.043), for LNMs in the groin compared to head or neck this was a trend (P=0.1). Positive FDG-PET and CT was the most important prognostic factor for MSS with a Hazard Ratio of 2.5. Disease free period for FDG-PET and CT negative patients was 46.0% (95%CI: 41.4%-50.2%) after 5 years. Conclusion FDG-PET and CT seem to be adequate staging tools for clinical stage III melanoma patients. Clinical stage III patients with no distant disease, as indicated by a negative FDG-PET and CT, show better MSS and DFP compared to previous studies. Moreover, patients with distant disease, as indicated by a positive FDG-PET and CT, also show better MSS compared to previous studies.

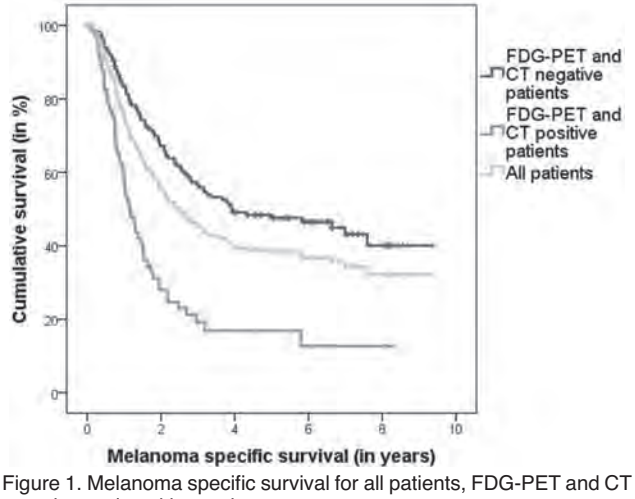

Figure 1. Melanoma specific survival for all patients, FDG-PET and CT negative and positive patients

P201

Stage IV Melanoma: Completely Resectable Patients are Scarce

K.P. Wevers,* H.J. Hoekstra. *UMCG Groningen, Groningen, Netherlands.*

Introduction. In melanoma, about one in five patients develops distant metastases and suffers a very poor prognosis. Common treatment options comprise surgery, systemic medical therapy, and radiotherapy, depending on the number, location, and the resectability of distant metastases. Previous studies suggested that surgery should be the first choice of treatment whenever complete surgical removal is feasible. The aim of the present study was to evaluate the extent of disease and resectability of melanoma patients presenting with stage IV disease at our institute. Methods. All melanoma patients diagnosed with stage IV between January 2011 and August 2012 were assessed for extent and resectability of their disease. Results. About half of 70 assessed patients had seven or more metastases at diagnosis, whereas 13 patients had only one metastasis. The vast majority (n=55, 78.6%) was ineligible for complete surgical resection. Six patients did receive complete surgery as initial stage IV treatment and in 9 patients incomplete surgery was performed. Widespread disease (n=44) and unresectable metastasis (n=11) were the most common reasons for refraining from complete surgery. (Table 1) Patients that underwent complete surgical resection suffered from a single pulmonary metastasis, two subcutaneous metastases, a single metastasis in the gallbladder, a single metastasis in the small bowel, a cerebral metastasis, and a single metastasis in the skull, respectively. Incomplete surgical resection was performed on varying grounds, like an invagination, bleeding or bowel obstruction due to one of multiple abdominal metastases, debulking of a symptomatic cerebral metastasis, and diagnostic excision of a (sub)cutaneous lesion in the presence of multiple distant lesions. There were no significant survival differences between the different stage IV treatment modalities. The median survival was 14.6 months, 17.3 months, and 14.5 months for surgery, systemic medical therapy, and radiotherapy, respectively. Conclusion. The results of the present study show that only a small proportion of patients diagnosed with stage IV melanoma are candidates for complete surgical resection at our institution.

Table 1. Assessment of complete resectability in 70 patients diagnosed with stage IV melanoma

Surgery as initial stage IV treatment	n	(%)
Complete surgery performed	6	(8.6)
Incomplete surgery performed	9	(12.9)
No surgery performed	55	(78.6)
Reason refrained from complete surgery: n=64		
Widespread disease	44	(62.9)
Unresectable metastases	11	(15.7)
Brain involvement	7	(10.0)
Patient in poor condition	1	(1.4)
Unknown	1	(1.4)

P202

Amelanotic Melanoma: Defining a Rare Disease Using the Surveillance, Epidemiology, and End Results (SEER) Registry

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Introduction: Amelanotic melanomas (AM) are a rare subset of melanomas, representing less than 5% of all melanomas in the few small series reported. They are defined by their loss of melanin expression, and given their scarcity and atypical appearance, frequently present as a diagnostic challenge. The differences in presentation of AM compared to pigmented melanomas (PM) and its prognostic implications are not well defined. Methods: The SEER registry (2004-2009) was queried for all cases of single, primary cutaneous melanoma with complete data, leaving N=54,194 for analysis. Univariate and multivariate analyses were performed and classification and regression tree (CART) analysis was used to risk stratify patients for nodal positivity. Kaplan-Meier curves were generated for survival analysis. Results: AM made up 0.3% (N=149) of study melanomas. There was no difference in gender (55% male) or anatomic location (51% extremity, 31% trunk, 18% head/neck) between patients with AM and PM. Patients with AM compared to PM were older (38% versus 23% ≥70 years old), and had lesions with increased thickness (71.2% versus 27.1% with T2-T4 lesions), level (73.9% versus 31.9% level IV/V), and ulceration (39% versus 11%) (all $p<0.0001$). Nodal positivity rate was 17% in patients with AM compared to

15.7% in PM patients. Level was associated with nodal positivity (p<0.0001). In CART analysis, level V stratified patients into two risk groups for nodal positivity (47% rate for level V versus 6% for II-IV). AM was associated with melanoma-specific death (OR=3.22, p<0.0001) in univariate analysis, but was not an independent predictor of survival (Table 1). Conclusion: AM is a rare subtype of melanoma. It presents more frequently in the elderly, as thicker and ulcerated lesions with higher level. Although associated with a worse melanoma-specific survival, it is not an independent predictor of survival when other pathologic factors are considered, suggesting that poorer outcomes may reflect more frequent diagnosis at an advanced disease stage. Greater awareness of this rare disease may lead to earlier diagnosis and improved outcomes.

Multivariate analysis - Hazard Ratios for Melanoma-Related Death (n=54194)

Predictors	Univariate Unadjusted		Multivariate Unadjusted	
	Hazard Ratio	p-value	Hazard Ratio	p-value
Thickness*	1.53	<0.0001	1.26	<0.0001
Ulceration	1.27	<0.0001	1.12	<0.0001
Level	4.27	<0.0001	2.41	<0.0001
Age at Diagnosis*	1.04	<0.0001	1.02	<0.0001
Sex				
Male	1.80	<0.0001	1.34	<0.0001
Site				
Head/neck	1.78	<0.0001	1.20	0.005
Trunk	1.18	0.004	1.34	<0.0001
Extremities	1.00	—	1.00	—
Amelanotic				
Yes	3.22	<0.0001	1.064	0.819
No	1.00	—	1.00	—

*Continuous variables.

P203

Determinants of Tumor Metastatic Potential in a Syngeneic Murine Melanoma Model S. Ganai,[1]* S.A. Khan,[1] A. Uppal,[1] S. Wightman,[1] N.N. Khodarev,[3] M.C. Posner,[1] R.R. Weichselbaum.[2] *1. The University of Chicago Medicine, Department of Surgery, Chicago, IL; 2. The University of Chicago Medicine, Department of Radiation Oncology, Chicago, IL; 3. The Ludwig Center for Metastasis Research, Chicago, IL.*

Introduction: Oligometastasis is a proposed state of restricted metastatic potential that has clinical implications related to likelihood of benefit from local therapies including metastastectomy. Defining the biology of oligometastasis is of interest to better select for and treat patients with limited metastatic disease. Methods: Subclones of B16 murine melanoma pulmonary metastases derived from in vivo passage were designated P2M5B ("oligo") and P2M3C ("poly"), with either limited or increased propensity to metastasize to lungs after systemic tail vein injection. Tumor growth and metastasis were studied in a syngeneic mouse model. Pooled metastases and cell lysates were profiled using Illumina mRNA and Taqman microRNA arrays. Results: There were no significant differences in tumor doubling time in vitro (11.7 vs. 12.0 hours, p<0.05) or in primary tumors (1.6±0.4 vs. 2.0±0.7 days, p<0.05) with comparisons between the oligo and poly cell lines. The median number of pulmonary metastases at three weeks after tail vein injection was 1 (interquartile range (IQR), 0-1) and 36 (IQR, 19-64) for the oligo and poly cell lines, respectively (p<0.0001). Differentially-expressed genes were noted in the IFN/STAT pathway in metastases derived from the poly cell line. Conclusions: Polymetastasis occurs independent of proliferation and may be influenced by IFN/STAT-pathway modulators, including upregulation of STAT3 and IFITM3. Further exploration of the role of JAK inhibition in regulating metastatic potential is warranted.

P204

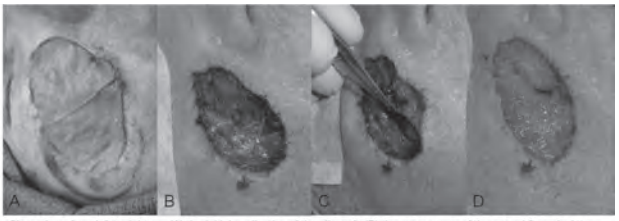
No Lymph Node Recurrence in Sixteen Melanoma Patients with a Starz I Involved Sentinel Node in Whom Completion Lymph Node Dissection was Omitted H.J. Veenstra, O.R. Brouwer, I.M. Van der Ploeg, B.B. Kroon, O.E. Nieweg.* *The Netherlands Cancer Institute, Amsterdam, Netherlands.*

Introduction: The Starz classification is based on both the location of a melanoma metastasis in the sentinel node and its growth pattern. This parameter was shown to be correlated with the presence of additional involved lymph nodes. The study was undertaken to explore the need for completion node dissection in patients with minimal involvement of the sentinel node. Its main purpose was to determine the long-term incidence of lymph node recurrence in patients with a Starz level I sentinel node (0.3 mm subcapsular invasion) in whom a completion lymph node dissection was omitted. The secondary aim was to examine whether recurrences elsewhere would develop. Methods: Between 2001 and 2007, sixteen melanoma patients had a sentinel node with a Starz level I metastasis. These were located in the axilla in seven patients, in the groin in six, in the neck in two and both in the groin and in the popliteal fossa in one patient. The patients did not undergo a completion lymph node dissection and were followed regularly for a median period of 66 months (range: 37-99 months). Results: None of the sixteen patients developed a lymph node recurrence during follow up. A local recurrence in the excision scar was seen in one patient and a second patient developed a satellite metastasis. The other patients remained free of disease. All patients were alive at the time of the final analysis. Conclusion: None of the patients with a Starz level I sentinel node metastasis developed a lymph node recurrence during the median follow up period of 66 months, despite the omission of a completion node dissection. This pilot study suggests that the risk of refraining from node dissection in such patients is so small that this option can be considered.

P205

Staged Excision of Lentigo Maligna and Lentigo Maligna Melanoma with the use of Irradiated Human Skin K. Vakharia,* R.I. Neves. *Plastic Surgery, Penn State Hershey Medical Center, Hershey, PA.*

Background: Published margin guidelines for lentigo maligna (LM) and lentigo maligna melanoma (LMM) are often inadequate for primary excision. Staged excision utilized for treatment, leads to low recurrence rates. This leaves the need for temporary coverage of an open wound until histologic confirmation of clear margins are obtained. The coverage should be affordable, easy to use, avoid contamination, and be painless. We present our institutional experience with an irradiated human skin allograft (IHSA). Methods: A retrospective review was performed of patients diagnosed with melanoma that underwent surgical excision over two years. Patients with pathology-confirmed LM or LMM and intra-operative IHSA placement were included. The procedures conformed to current published National Comprehensive Cancer Network margin guidelines. Patients removed their surgical dressing after 24 hours, allowed it to air dry, and showered after 48 hours. No further dressing changes were required. Results: A total of 32 patients were included; of these, sixteen patients (50%) had more than one procedure done for positive margins, and five patients (15%) had three or more procedures. IHSA was utilized in a total of 55 operative cases. Clinic notes were reviewed for outcomes of the surgery, which revealed that in all of these cases the graft was adherent. Only one patient experienced a wound infection with drainage requiring oral antibiotics. Most patients had no complaints or difficulties with the allograft and complained of minimal pain. The cost of one application of IHSA on average is $350, significantly less than the cost of daily wet to dry dressing changes with visiting nurses which is estimated to be $839 for 10 visits. Conclusion: The use of staged procedures with histologic confirmation of margins is safer for LM, and LMM resection. With IHSA, patients do not require daily dressing changes or visiting nurses, decreasing costs of postoperative management. IHSA use also offers low rates of wound complications. In skin oncology, irradiated human skin provides surgeons and patients with a beneficial, affordable, and safe biologic dressing for staged excision procedures.



Shown here from left to right are (A) the initial application of the allograft, (B) the appearance of the wound 2 weeks later, (C) removal of the dried graft, and (D) unveiling of a healthy wound bed underneath.

P206

IL-35 Promotes Melanoma Growth by Promoting Proliferation and Inhibiting Apoptosis M.B. Nicholl,* Y. Fang, K. Cook, E. Herrick. *Surgery, University of Missouri, Columbia, MO.*

Introduction: IL-35 is recently described cytokine which may mediate the inhibitory effects of regulatory T cells (Treg). While IL-35 inhibits effector T cell function, it promotes Treg proliferation, suggesting its complex role in

cell growth. Our previous study has shown that IL-35 directly enhances pancreas cancer growth, however, its effect on melanoma is unknown yet. In this study, we examined its effect on proliferation and apoptosis of a melanoma cell line, SK-Mel-5. Methods: Clonogenic survival assay, immunohistochemistry, TUNEL staining, proliferation and caspase-3 activity kits were used to evaluate the effects of IL-35 on cell survival, proliferation and apoptosis. We further investigated the possible molecular mechanisms by using RT-PCR, IHC and Western blot. Results: We found that the percentage of colonies, PCNA+ cells and the OD value of SK-Mel-5 cells were significantly increased in the presence of IL-35. TUNEL+ cells and the relative caspase-3 activity were both decreased in the presence of IL-35. Mechanistic investigation showed that the pro-proliferative effect of IL-35 correlated with downregulation of anti-proliferative molecule p27 and upregulation of proliferative molecule cyclin B. The anti-apoptotic effect of IL-35 correlated with upregulation of anti-apoptotic molecule Bcl-2, FLIP and survivin. Conclusions: These results suggest that, consistent with our previous findings in pancreatic cancer, IL-35 also directly enhances melanoma growth by promoting proliferation and inhibiting apoptosis. These findings extend our previous study and further support a second possible mechanism by which Treg may promote tumor growth.

P207

Intraoperative Imaging of Pleural Malignant Mesothelioma Improves Disease Detection O. Okusanya,* B.F. Judy, B. Madajewski, J.G. Quatromoni, J. Predina, S. Singahl. *Surgery, Univ of Penn, Philadelphia, PA.*

Background: Malignant mesothelioma is a devastating disease of the pleural lining of the lung which is managed with trimodal therapy including surgery, chemotherapy and radiation. The most important prognostic indicator for cure is a complete resection with no residual disease. However, intraoperative detection of retained cancer cells after surgery is challenging, and residual disease continues to be the most common cause of local failure. We hypothesized visual enhancement of implants using near-infrared imaging could potentially identify tumor deposits during surgery. Methods: Flank tumors using the AB12 and AE17 mesothelioma cell line were grown in syngeneic immunocompetent mice. At the time of surgery, these mice were then injected with indocyanine green, a near-infrared fluorescent dye that localizes to mesothelial tumors through the enhance permeability and retention effect. The tumors were then randomized to surgery with or without intraoperative imaging. Results: Over 7 experiments, 80 animals underwent complete surgical resection based on visual and palpable clues. Within one week of surgery with no intraoperative imaging, 17 out of 40 mice (42%) developed recurrences within 3 weeks. In the treatment group, intraoperative imaging after surgery detected residual disease in 13 out of 40 animals that were thought to have no evidence of retained tumor cells. Only 2 of 40 mice that were deemed cured by surgery combined with intraoperative imaging recurred (Figure 1). Conclusions: The results suggest that near-infrared examination of the surgical wound after curative resection can potentially enable the surgeon to locate residual disease. Combining targeted dyes and novel detection technology may prove effective in detecting and eliminating residual tumor burden in a wide range of solid tumors during surgery.

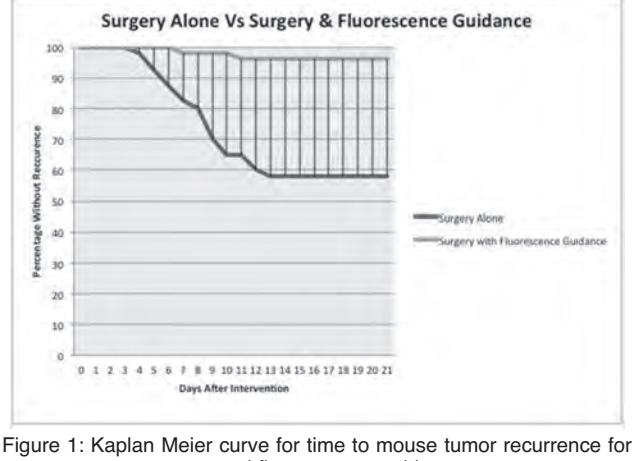


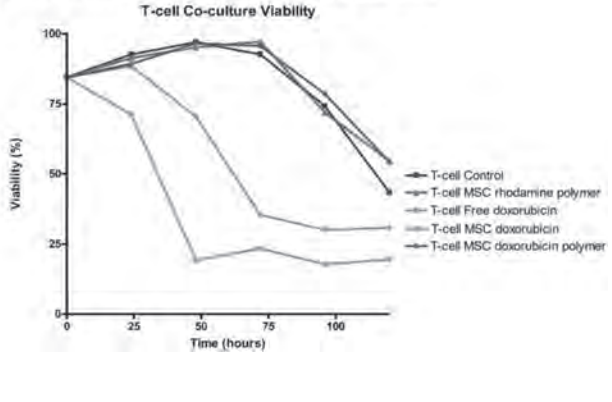
Figure 1: Kaplan Meier curve for time to mouse tumor recurrence for surgery versus surgery and fluorescence guidance.

P208

A Novel Approach to Targeted Oncologic Therapy - Co-Culture Viability of Polymer Prodrug Conjugation to Mesenchymal Stem Cells K.E. Wong,[1]* N. Panzarino,[3] S. McRae,[4] R. Arenas,[1] S. Schneider,[2] T. Emrick.[4] *1. Department of Surgery, Baystate Medical Center, Springfield, MA; 2. Pioneer Valley Life Sciences Institute, Springfield, MA; 3. Molecular and Cellular Biology Program, University of Massachusetts, Amherst, MA; 4. Polymer Science and Engineering Department, University of Massachusetts, Amherst, MA.*

Background: Conjugation of polymers to chemotherapeutic agents can reduce their systemic side effects, alter the mechanism of drug release, and provide new opportunities for treating cancer. Conjugation of polymer prodrugs to tumor homing cells, such as mesenchymal stem cells (MSCs), could provide a vehicle for actively targeted delivery of polymer prodrugs. Here we address whether MSCs can be engineered to deliver prodrugs in a time or pH dependent manner allowing for killing of nearby cells. We used T cells as a doxorubicin-sensitive cell population for testing drug release in co-culture experiments. Methods: MSCs were conjugated to doxorubicin polymer prodrug, a rhodamine-containing polymer, and free doxorubicin in a 10uM solution for 15 minutes. The conjugated MSCs were then co-cultured with T-cells. T-cells were also cultured alone in media containing a 1uM concentration of free doxorubicin for comparison. The viability of T-cells was assessed through the use of a cell counter. Results: T-cell viability was reduced when cultured alone in media containing free doxorubicin and when co-cultured with MSCs conjugated to free doxorubicin. T-cells co-cultured with MSCs conjugated to both rhodamine polymer and the doxorubicin polymer prodrug, had similar viability when compared to T-cells control cultures (Figure 1). Conclusion: MSCs conjugated to doxorubicin were resistant to death-inducing effects of the drug. However, over time MSCs released doxorubicin resulting in a time dependent decreased viability of neighboring T-cells. Polymer controls conjugated to MSCs had no effect on T-cell viability indicating that this was a drug dependent effect. MSCs, therefore represent an potential vehicle for actively targeting drug delivery. Future work will focus on developing methods for releasing the drug upon successful delivery to targeted tumor cells in vivo.

Figure 1: Viability of T-cells co-cultured with conjugated MSCs



P209

Developing Irradiated Autologous Tumor Cells as a Novel Delivery Vehicle for Anti-Cancer Therapy S.R. Grobmyer,[2]* G. Zhou,[1] P. Sharma,[1] M. Hahn,[1] B. Moudgil,[1] S. Brown.[3] *1. Surgery, University of Florida, Gainesville, FL; 2. Cleveland Clinic, Cleveland, OH; 3. DuPont Central Research and Development, Wilimington, DE.*

Introduction: Engineered nanoparticles (NP) hold significant promise for treating cancer but delivering NP to sites of cancer remains a significant challenge. The tumor self-seeding theory suggests that circulating tumor cells (CTCs) have a predilection for established sites of tumor in vivo. Studies suggest that seeding of tumor cells is mediated by tumor derived IL-6 and IL-8 (chemotaxis) as well as Fascin-1 (infiltration). We broadly seek to exploit irradiated, non-replicative tumor cells as biological vehicles for delivering NP to sites of cancer. In this study, we hypothesize that irradiation of cancer cells (25Gy) renders them non-replicative while maintaining their ability to undergo chemotaxis, invasion, and endocytosis of NP. Methods: MDA-MB-

231 breast cancer cells in culture were irradiated (25Gy) and compared to non-irradiated control cells. Tumor cell proliferation, NP uptake, chemotaxis, and invasion were compared in irradiated and control cells in vitro. Novel, biocompatible silica NP of 50 nm diameter and containing a fluorescent near-infrared dye were synthesized for these studies. Results: Following irradiation MDA-MB-231 cells were viable but non-proliferative. Irradiation of MDA-MB-231 cells did not alter the ability of cells to endocytose NP compared to control cells. Irradiated and NP loaded irradiated cancer cells undergo chemotaxis similar to control cancer cells. FSCN-1 release from cells was increased in irradiated cells, and the ability of cancer cells to invade the extracellular matrix was also increased in irradiated cancer cells. Conclusions: Irradiated cancer cells (25Gy) are viable but non-proliferative suggesting they could be used safely as NP delivery vehicles in vivo. Irradiated cancer cells also endocytose NP similar to non-irradiated cancer cells. Irradiation does not block the ability of cancer cells to undergo chemotaxis or invasion—the two fundamental properties of self-seeding cancer cells. These findings suggest a novel paradigm for exploiting tumor self-seeding for delivering NP to cancer in vivo.

P210

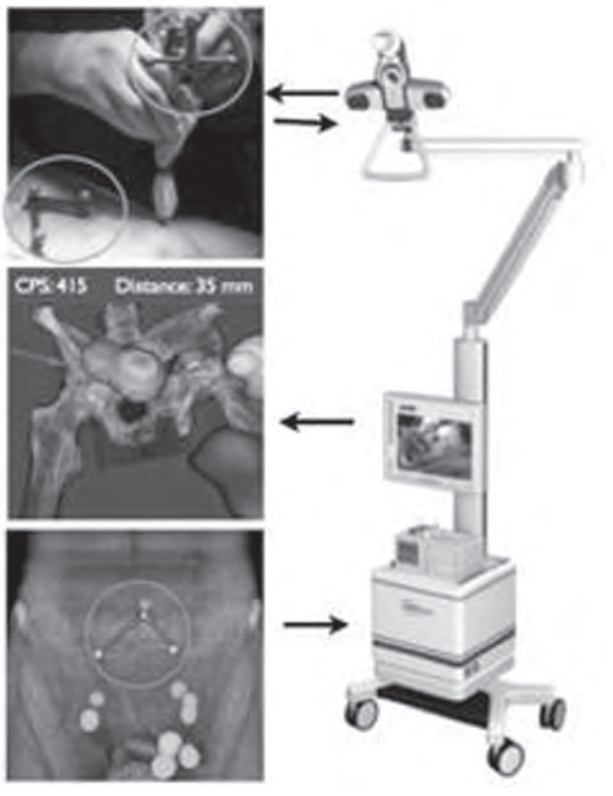
Extended Survival in the Elderly Undergoing Cytoreductive Surgery/Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC)
S. Shankar,* M. Sittig, C. Nieroda, R. MacDonald, V. Gushchin, A. Sardi. *Surgical Oncology, Mercy Medical Center, Baltimore, MD.*

Introduction: Peritoneal carcinomatosis is currently treated with CRS/HIPEC, which is an aggressive and lengthy surgery. In general, age has been considered a relative contraindation to some aggressive therapies. We hypothesize selected elderly patients can undergo CRS/HIPEC without increased morbidity or mortality. Methods: Retrospective analysis of a prospective database of 288 patients undergoing 329 CRS/HIPEC procedures from January 1999 to April 2012 yielded 53 patients ≥ 65 years of age (18%). Descriptive statistics for histology, age at surgery, peritoneal cancer index (PCI), cytoreduction score (CC), mean hospital stay, morbidity, mortality, and follow up are reported. Survival estimates were calculated using Kaplan Meier method. Results: Mean age at diagnosis was 69 (range 52-79) and at surgery 70.5 (range 65.5-80.9). Mean follow up was 29 months. Histology was 67% appendiceal (36/53), 13.2% primary peritoneal (7/53), 7.5% malignant mesothelioma (4/53), 5% colonic (2/53), 3% ovarian (2/53) and 1.8% sarcoma (1/53), respectively. Overall PCI score was >20 in 77.3%. Forty-six patients (86.7%) had complete cytoreduction (CC-0/CC-1). Mean hospital stay (LOS) was 16.5 days, with one in hospital death and one perioperative death within 30 days. Thirty-seven percent (20/53) had one grade 3 complication and 24.5% (13/53) had two or more. Fifty-four percent of patients (29/53) are alive. Estimated 1, 3, and 5 year survival rates were 75.8%, 53.4% and 45.5%, respectively. Of 36 patients with appendiceal tumors, 61.1% are alive with mean age at diagnosis of 69.2 (range 57.5-79.8) and at surgery of 70.5 (range 65.5-80.9). Mean follow up was 29.5 months. Histology was DPAM in 44.4% (16/36) and PMCA in 55.5% (20/36). Overall PCI score was >20 in 83.3%. CC-0/CC-1 was achieved in 83.3% (30/53). Mean LOS was 16.4 days. Estimated 1, 3 and 5 year survival rates were 82.5%, 62.1% and 49.7%, respectively. Conclusion: Selected patients ≥ 65 years of age who underwent CRS/HIPEC had extended and meaningful survival with acceptable morbidity and mortality. Age should not be a contraindication to CRS/HIPEC.

P211

Feasibility of Image Guided Sentinel Node Biopsy using Augmented Reality and SPECT/CT-based 3D Navigation
O.R. Brouwer,[1]* N. Van den Berg,[2] H. Mathéron,[1] O.E. Nieweg,[1] S. Horenblas,[1] H. Van der Poel,[1] T. Wendler,[3] R. Valdés Olmos,[1] F. Van Leeuwen.[2] *1. Nuclear Medicine, Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, Netherlands; 2. Leiden University Medical Center, Leiden, Netherlands; 3. Technische Universitat Munchen, Munich, Germany.*

INTRODUCTION Vital dye and the gamma ray detection probe are the standard tools for sentinel node (SN) biopsy in patients with breast cancer or melanoma. Head and neck cancer, gynaecological cancers and urological cancers have more complex lymph drainage patterns and are associated with a more intricate anatomy. SN biopsy for these cancers requires more sophisticated technology. The innovative DeclipseSPECT system (SurgicEye, Munich, Germany) enables intraoperative navigation based on the preoperative images. This study aims to explore the clinical feasibility and accuracy of this approach. METHODS Ten patients with penile carcinoma and three with melanoma of a leg were included. After injection of radiolabeled colloid, preoperative conventional scintigraphy and SPECT/CT were performed with a reference target for orientation fixed on the patient. The SPECT/CT images were loaded into the navigation system. Immediately preceding the operation, a sterile reference target was fixed at the same location on the patient. A second reference target was attached to the gamma ray detection probe to generate the intraoperative data that enables navigation of the probe towards its target. This information is fused with the preoperative images, generating a virtual view of the SPECT/CT images from the perspective of the probe on the video screen. Navigation with the probe was performed in each patient prior to the incision in order to determine the accuracy with which the SN could be localized through the intact skin with the conventional probe as the gold standard. RESULTS The 3D SPECT/CT navigation was easy and quick. The mean localization error was 5 mm (range 0-10 mm). In two patients, 3D SPECT/CT navigation pointed to the exact same location as the conventional probe. CONCLUSION Intraoperative navigation based on preoperatively acquired SPECT/CT images is feasible. The accuracy of navigation is influenced by the accuracy and consistency with which the reference target can be placed on the patient. This navigation approach may have high potential in laparoscopic applications and opens the way to include PET/CT and MRI in the guidance process.



P212

SIAH as a Promising Biomarker Predictive of Cancer Cell Response to Effective Chemotherapy
V. Zheleva,* M. Bian, R.R. Perry, A.H. Tang. *Eastern Virginia Medical School, Norfolk, VA.*

Introduction: The EGFR/HER2/K-RAS signaling pathway is pivotal in driving cell proliferation, tumor progression and metastasis. SIAH (seven-in-absentia human homologue) is the most downstream "gatekeeper" essential for proper ERBB/K-RAS signal transduction and tumor cell growth and survival. SIAH is expressed in all proliferating tumor cells. We hypothesize that

effective chemotherapy leads to decreased SIAH expression in cancer cells, which correlates with decreased cell viability and reduced tumor growth. Methods: Using immunofluorescence staining, endogenous SIAH expression was identified in lung cancer cells (A549) and triple negative breast cancer cells (MDA-MB-231) pretreated with increasing concentrations cisplatin/paclitaxel and doxorubicin/paclitaxel, respectively. Flow cytometry was also used in A549 to verify and validate the reduction in SIAH expression in response to chemotherapy. Chemotherapy efficacy was quantitatively determined through cell proliferation assays via cell counting and anchorage-independent tumor growth in soft agar. Experiments were performed in quadruplicate. Results: In response to increasing doses of chemotherapy, the percentage of A549 and MDA-MB-231 cells expressing SIAH decreased significantly – results derived by immunofluorescence staining (Figure 1) and confirmed by flow cytometry for A549 (data not shown). There was a corresponding significant decrease in cell survival in response to standard chemotherapy when compared to untreated cells (Figure 1) and a marked reduction in tumor growth in soft agar assays (data not shown). Conclusions: SIAH expression in human cancer cells decreases significantly in response to effective chemotherapy. Decreased SIAH expression corresponds to decreased cell survival and diminished tumorigenesis. SIAH shows promise as a new and predictive biomarker of chemotherapy response. Future work studying neoadjuvant-treated human tumor specimens will aim to validate that SIAH is an excellent biomarker predictive of chemotherapy response in the clinical setting.

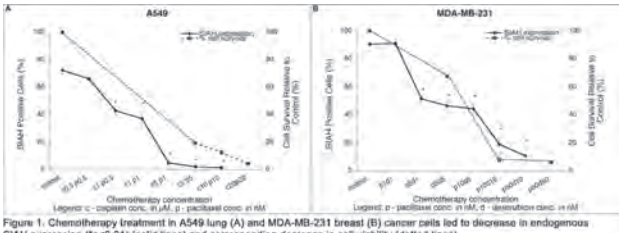


Figure 1. Chemotherapy treatment in A549 lung (A) and MDA-MB-231 breast (B) cancer cells led to decrease in endogenous SIAH expression (*p<0.01) (solid lines) and corresponding decrease in cell viability (dotted lines).

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The Role of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Patients with Primary Peritoneal Carcinoma with Failed Conventional Treatment S. Shankar,* M. Sittig, C. Nieroda, R. MacDonald, V. Gushchin, A. Sardi. *Surgical Oncology, Mercy Medical Center, Baltimore, MD.*

Introduction: Primary peritoneal carcinoma (PPC) is a rare tumor, traditionally treated with surgical debulking and systemic chemotherapy (SC) with a five-year survival rate of 30%. We hypothesize that even following failed conventional therapy, treating PPC as a regional disease with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) will improve long term survival. Methods: A retrospective study of a prospective database of 293 patients with peritoneal surface malignancies underwent 334 HIPEC surgeries. Nineteen patients with advanced PPC were identified. 17 underwent CRS/HIPEC and adjuvant SC and 2 patients underwent CRS/HIPEC without adjuvant SC. Histology of disease, peritoneal cancer index (PCI) and cytoreduction scores (CC score) were identified and reviewed using Kaplan Meier survival analysis. Results: Mean age was 60 years (range: 40-75). Mean follow up was 38.4 months (range: 0.6–206.2). Of the 19 patients, 10 had failed previous surgical debulking with SC treatment (9 combination taxane/platinum-based regimen and 1 5-Fluorouracil/leucovorin regimen). One patient had recurrence after receiving SC alone and 1 had recurrence after debulking alone. Seven patients had no interventions prior to CRS/HIPEC. The overall PCI score was > 20 in 63% of patients. 18 patients (95%) had complete cytoreduction (CC-0/CC-1). Thirty-seven percent of patients had 1 grade 3 complication and 26% had 2 or more. Hospital mortality rate was zero. One perioperative death occurred within 30 days due to unknown causes. Currently, 14 patients (74%) are alive, 2 living with disease, and 12 without. Five disease related deaths occurred. The overall 1, 3, and 5 year actuarial survival rates are 94%, 69%, and 55%, respectively. Conclusion: CRS/HIPEC and adjuvant SC provides 5 year survival rate higher than previously reported for PPC patients that have received conventional therapy with surgical debulking and SC. A randomized prospective study using CRS/HIPEC and adjuvant SC in a larger population is advocated.

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Drain Amylase Accurately Predicts Anastomotic Leak after Esophagectomy J.S. Hill,* E.M. Hanna, S. Hurley, M. Reames, J.S. Salo. *Carolinas Medical Center, Charlotte, NC.*

Esophagectomy is considered the only curative approach in patients with esophageal cancers without locally advanced or metastasis. Anastomotic leak can lead to significant morbidity and mortality. CT esophagram (CTE) is a sensitive method of evaluating for leak; however this test carries with it financial cost and radiation exposure. This study evaluates the utility of drain amylase in the prediction of anastomotic leak. Fifty-nine patients underwent esophagectomy between 3/10 and 8/12; serial drain amylases and CTE were obtained in 50. Leak was defined by extravasation of contrast or the presence of empyema on CTE. Elevated drain amylase was defined as any level > 400 IU/L. Chi-square and descriptive statistics were performed and the sensitivity of drain amylase >400 IU/L in predicting leak was calculated. A minimally invasive esophagectomy was performed in 47, and an open Ivor-Lewis in 2 and a minimally invasive Ivor-Lewis in 1. Stapled intra-thoracic anastomoses were performed in 47, 3 had a cervical anastomoses. Average age was 61 years and 84% were males. Leak occurred in 6 patients (12.5%). One patient with a late leak was excluded from analysis as they did not have concurrent drain amylase values. This patient had low amylase levels and a normal CTE, though later presented with leak. The overall peri-operative mortality rate was 4.2% (2/48). Mortality in the non-leak and leak cohorts were 0% & 33% . Drain amylase was an accurate marker of anastomotic leak. Of 6 patients with an elevated drain amylase, 5 had an anastomotic leak (sensitivity 83.3%). 40/41 patients with low drain amylase had no leak. Using a cut-off value of 400 IU/L, the negative predictive value of drain amylase in predicting leak after esophagectomy was 97.6% (95%CI; 85.6, 99.9). Drain amylase is a simple and inexpensive test that has excellent sensitivity and negative prediction for the detection of anastomotic leak after esophagectomy. To our knowledge, this is the first study to demonstrate this finding. Routine evaluation of drain amylase may safely replace CTE in the management of patients after esophagectomy, thus reducing radiation exposure and overall cost.

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A Novel Humanized Monoclonal Antibody to SFRP2 Inhibits Wnt-Signaling in Glioblastoma Cells J. Samples,[1]* S. Snyder,[1] R. Mumper,[3] D. Ketelsen,[1] C. Patterson,[2] N. Klauber-Demore.[1] *1. Surgical Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC; 2. Lineberger Comprehensive Cancer Center, Chapel Hill, NC; 3. School of Pharmacology, Chapel Hill, NC.*

Background: Antagonizing secreted frizzled related protein 2 (SFRP2) with a mouse monoclonal antibody (MAb) inhibits breast cancer and angiosarcoma growth in vivo and inhibits activation of β-catenin and NFATc3 in vitro. Overexpression of SFRP2 in glioma cells promotes tumor growth in vivo. Our objective was to generate a humanized SFRP2 MAb and to elucidate whether SFRP2 antagonism inhibits WNT signaling in glioblastoma. Methods: Antibody humanization: Chimeric antibodies and combinations of composite heavy and light chains were expressed in NS0 or HEK293 cells and tested for binding to SFRP2 by ELISA. The MAb selected for production was tested for its ability to induce CD4+ T cell responses as measured by proliferation against a panel of 22 HLA-typed donors compared to a control. Wnt signaling: When β-catenin and NFATc3 are activated they translocate to the nucleus. We investigated Wnt activation in U87 cells by treating them with 200ug/ml of hSFRP2 MAb or IgG1 control. Nuclear extracts were harvested and western blot was performed probing for NFATc3 and β-catenin. Results: Immunogenicity: Positive CD4+ T cell proliferation responses were observed against the control antigen. No responses were seen to the hSFRP2 MAb indicating very low immunogenicity. Wnt signaling: Western blot analysis of control U-87 cells demonstrated high nuclear protein levels of β-catenin and NFATc3. Exposure to hSFRP2 MAb resulted in a large decrease in nuclear β-catenin and NFATc3 (Fig. 1). Conclusion: A humanized SFRP2 MAb inhibits glioblastoma activation of β-catenin and NFATc3. Further investigation into the efficacy of hSFRP2 MAb for glioblastoma is warranted.

Fig 1. Western blot analysis of nuclear extracts from U87 glioblastoma cells show decreased expression of NFATc3 and β-Catenin in cells treated with hSFRP2 compared to IgG Control. This demonstrates that hSFRP2 affects Wnt-Signaling by decreasing nuclear translocation of β-Catenin and NFATc3.

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Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC): 100 Consecutive Patients in an Asian Institution G. Tan,[1]* M. Teo,[2] C. Lim,[2] D. Ng,[2] C. Tham,[2] K. Soo.[2]
1. General Surgery, Singapore General Hospital, Singapore, Singapore; 2. 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 experience with the procedure and evaluate the overall and disease-free survival rates in 100 consecutive patients. Method: Data was prospectively collected from 100 consecutive patients with peritoneal carcinomatosis treated by CRS and HIPEC at the National Cancer Centre Singapore between April 2001 and May 2012. Our primary end points were overall and disease-free survival. Results: Of the 100 patients, 84% were of Chinese ethnicity, 3% were Malay, 6% were Indian and 7% were of other ethnicities. Primary tumors were ovarian cancer (n=39), colorectal cancer (n=28), primary peritoneal (n=6), appendiceal cancer (n=20), and mesothelioma (n=7). Median follow up duration was 21 months. At 3 years, the disease-free survival was 32.9% and overall survival was 59.1%. Factors influencing overall and disease-free survival were cytoreductive score, primary cancer, and disease free interval of more than 12 months on univariate analysis. The only factors that remained significant for prognosis after multivariate analysis were primary cancer and cytoreductive score. 30-day Morbidity was 56% and there were no 30-day inpatient mortalities. Conclusion: CRS and HIPEC can be safely carried out in Asian patients with peritoneal carcinomatosis from ovarian, colorectal, appendiceal, mesothelioma and primary peritoneal origins. Overall, the ovarian, appendiceal, mesothelioma and primary peritoneal cancer patients tended to do better than the colorectal patients, but careful patient selection in order to ensure that optimal cytoreduction can be achieved is essential for the success of this procedure.

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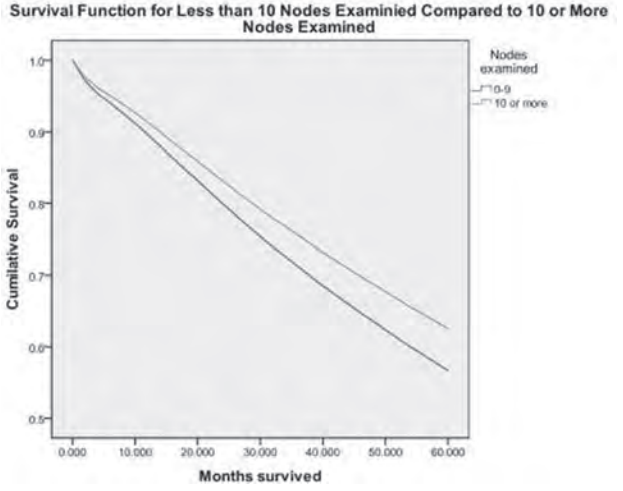
Limited Thoracic Lymphadenectomy Worsens Survival in 55,122 Patients with Resected Stage I Non-Small Cell Lung Cancer C.M. Pezzi,[1]* E. Gay,[2] N. Kulkarni,[1] J.B. Putnam.[3] *1. Surgery, Abington Memorial Hospital, Abington, PA; 2. American College of Surgeons, National Cancer Data Base, Chicago, IL; 3. Vanderbilt University Medical Center, Nashville, TN.*

Introduction: The benefit of thoracic lymphadenectomy in the treatment of surgically resectable non-small cell lung cancer (NSCLC) continues to be debated. Quality measures indicate a minimum threshold number of lymph nodes (LN) should be resected for adequate staging of several other solid tumors. We hypothesized a relationship between the number of negative LN removed for patients with node-negative pathologic Stage (pStage) I NSCLC and survival. Methods: The National Cancer Data Base (NCDB) was queried for pStage I NSCLC patients treated between 1998 and 2003. These dates were chosen to allow for five years of follow-up. Patients were grouped by the total number of negative LN removed (1-4, 5-8, 9-12, 13-16, and >=17 LN). Patients who had <10 negative LN removed were also compared to those with >=10 LN examined. A Cox regression analysis was performed and hazard ratios (HR) calculated, with 95% confidence intervals (CI) for factors predicting mortality. Results: Of 482,392 patients with NSCLC reported to the NCDB during the study period, 55,122 (11.4%) were pStage I, had at least one LN removed, and the exact number of LN removed was reported. Lobectomy was performed in 47,391 (86%), sublobar resection in 4,868 (8.8%) and pneumonectomy in 2,544 (4.6%). The number of LN removed increased with tumor size and with the extent of resection. Factors associated with an increased risk of mortality included pStage IB, male gender, higher grade, and fewer LN removed. Patients with <10 LN removed had a HR of 1.21 (95% CI 1.18-1.25) times greater chance of death than patients with >= 10 LN examined. Patients who had >=17 LN removed had a HR of only 0.78 (95% CI 0.74-0.82) compared to patients with 1-4 LN examined. Patients having 1-4 LN removed accounted for 19,665 (35.7%) of all patients. Conclusion: Survival of pStage I NSCLC patients is higher when 10 or more LN are removed. The surgical treatment of early stage NSCLC should include thoracic lymphadenectomy with 10 or more LN resected.



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Planned Esophagectomy after Neoadjuvant Treatment versus Salvage/Delayed Esophagectomy J.A. Alosi,[1]* J.P. Wilson,[2] S. Yendamuri,[1] E. Dexter.[1] *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. Sentara Surgery Specialists, Newport News, VA.*

INTRODUCTION: Trimodal therapy is the gold standard for treating esophageal cancer, yet not all patients are good surgical candidates. Retrospective studies suggest salvage esophagectomy as a viable option for those that fail definitive chemoradiation therapy, particularly with squamous cell carcinoma (SCC). We evaluated our experience with salvage/delayed esophagectomy in an adenocarcinoma (adeno) predominant population. METHODS: This is a single institution retrospective review of patients treated for esophageal cancer from January 1, 1990 through May 1, 2012. Characteristics and outcomes of patients who underwent planned esophagectomy following neoadjuvant chemoradiation were compared with patients that underwent salvage/delayed esophagectomy. Univariate and multivariate analyses examined the relationship of timing of surgery with overall survival. RESULTS: Of the 180 patients who underwent esophagectomy (86% adeno), 44% had tumor downstaging, and 26% had a complete pathologic response. Surgical mortality was 5%, recurrence rate was 38.5% and anastomotic leak rate was 12.7%. 157 (88% adeno) patients underwent planned trimodal therapy; 23 (83% adeno) patients underwent salvage esophagectomy after definitive chemoradiation or delayed esophagectomy (>90d after chemoradiation). Although the salvage/delay group had higher clinical stage, the two groups were similar in pathologic stage, type of surgery, R0 resection rate, histology, grade, length of stay, and blood loss. Univariate analysis showed no difference in complication rates or perioperative mortality. There was no difference in recurrence free survival. However, overall survival between the two groups was statistically significant and favored non-delayed surgery (median survival 42months vs. 18 months; p<.0001). CONCLUSIONS: Post-operative morbidity and mortality are similar for patients undergoing salvage/delayed and planned esophageal resection. In the face of persistent or recurrent esophageal cancer after chemoradiation, patients with adenocarcinoma as well as SCC should be offered salvage/delayed esophagectomy with the understanding that the survival of these patients is not as good as non-delayed surgery.

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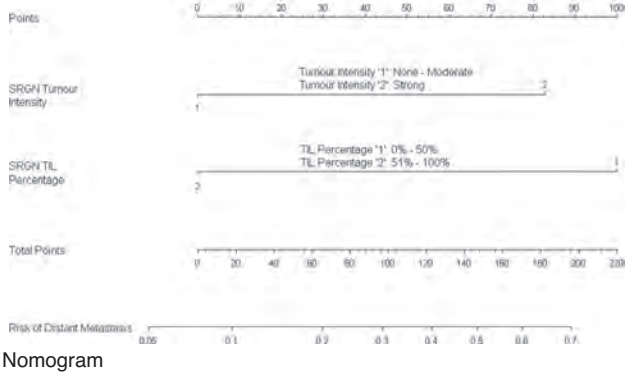
Serglycin Expression is an Independent Marker of Distant Metastases in Nasopharyngeal Carcinoma C.S. Chia,* W. Ong, X. Li, Y. Soong, F. Chong, H. Tan, K. Soo, C. Qian, B. Teh, N. Iyer. *Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore.*

Objective: Nasopharyngeal carcinoma(NPC) is endemic in South-East Asia and has high propensity for metastasis. Recent data suggests that Serglycin is an important mediator of tumor spread. Our aim is to determine whether Serglycin expression can used to predict for distant metastases. Methods: From our database of patients treated between January 2004-October 2008, 112 patients with NPC were selected with complete clinico-pathologic data and adequate tissue for immunohistochemistry(IHC). Serglycin expression(based on IHC) was assessed based on the following parameters:percentage of tumor-cells expressing Serglycin, staining intensity, percentage of tumour-infiltrated lymphocyte(TIL) expressing Serglycin and TIL-staining intensity. Univariate and multivariate analyses were performed and a nomogram incorporating predictors was constructed. Results: Risk factors for distant metastasis included gender, smoking status, tumour intensity and TIL percentage for Serglycin. The odds of distant metastasis was 4.13 and 0.18 in patients with strong tumour intensity and >50% TIL percentage,respectively. Based on the nomogram, patients were stratified into 2 prognostic groups. The proportion of distant metastases in the high-risk group(based on strong tumour intensity and ≤50%TIL percentage) was 78% versus 19% in the low risk group($p<0.001$). Conclusion: NPC patients with tumors showing strong tumour intensity and low TIL percentage with serglycin may be at high risk for distant metastasis.



Nomogram

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A Novel Small Portable Imager of Fluorescence (SPIF) For Intraoperative Imaging of Lung Tumors B. Judy,[1]* O. Okusanya,[1] E.T. Segal,[1] J.G. Quatromoni,[1] B. Madajewski,[1] D. Holt,[2] S. Singahl.[1] *1. University of Pennsylvania School of Medicine, Philadelphia, PA; 2. University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA.*

Introduction: Up to 20% of patients that undergo "curative" surgical resection leave the operating room with cancer cells at the margins, satellite lesions or lymph nodes. Optically visible fluorescent dyes exist that can visually enhance tumor deposits, however, require complex imaging systems which have limited utility in the operating room. Our group hypothesized a light-weight, hand held NIR camera system would be adaptable in the operating room for real-time intraoperative imaging. Methods: Over several months, we developed several CCD cameras with a broad range of filters, narrow band light sources and tracers to examine murine and canine tumor tissue. Once constructed, we tested our imaging system on three canine patients with spontaneous lung tumors scheduled for surgery. At the time of operation, each had their lung cancers imaged in vivo and on the back table. Histopathology was used to confirm the diagnosis. Results: Ultimately, we used a CCD camera mounted on a metal plate with a reticulating 760nm bandpass filter and a 720nm LED spotlight (The Small Portable Imager of Fluorescence — SPIF). The images captured by the camera were integrated with commercially available software. The dogs were injected with indocyanine green prior to their planned pulmonary resections. All 3 patients underwent uneventful pulmonary resection with intraoperative imaging with no adverse events. All tumors were fluorescent and could be easily visualized during imaging (Figure 1). All findings were consistent on final pathology. Conclusion: The results suggest that near-infrared imaging using our cost effective portable system can accurately and reliable detect canine lung cancer. This imaging technology has the potential to dramatically improve the care for patients with cancer who undergo for surgery and we show that it can readily and efficiently be implemented.

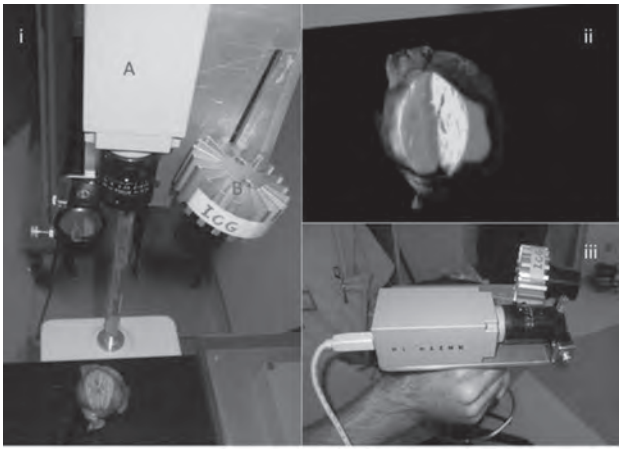

Figure 1: (i) SPIF Mounted on ring stand with explanted canine tumor. Image shows (A) CCD Camera (B) LED spotlight (C) NIR light filter (ii) Fluorescence image overlay of tumor (iii) Handheld configuration

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An Improved Hemicorporectomy Technique M.B. Janjua,* D.C. Crafts, F.E. Johnson. *Saint Louis University Medical Center, St. Louis, MO.*

Introduction: The first attempted hemicorporectomy, also known as translumbar amputation (TLA), was reported in 1960. The first TLA with survival was performed in 1961. It is a life-saving procedure initially designed for carefully selected patients with otherwise terminal cancer. It is the only operation in which the spine is electively divided. The first attempts featured a one-stage procedure but TLAs are usually performed in 2 stages now. In the 2-stage strategy, the first stage entails fecal and urinary diversion and all other procedures deemed useful. The second stage is the amputation. About 58 cases are reported. Several techniques have been described. We report our experience with 4 patients, all done in 2 stages. Methods: We accessed the PubMed/MEDLINE online database using the keywords hemicorporectomy and translumbar amputation. We reviewed technical details of the operations in our series. Results: We found 15 articles that described technical features. The anterior approach is familiar to surgeons and suitable for the first stage. Some reports featured an initial supine position for the second stage; one featured the decubitus position. We utilized a supine position for our first 2 cases but found that this led to excessive blood loss and a long operative time, both caused by the obligatory vertebral corpectomy. We therefore switched to an initial prone position for the second stage in next 2 cases. This allowed us to easily expose and resect the posterior bony elements (which entails minimal blood loss), open the dura, divide the cauda equina, close the dura, and mark the disc to be divided later. Then the operative wound is covered with a sterile dressing and the patient is turned to the supine position, the aorta and vena cava are divided, and the spine is divided through the previously marked intervertebral disc. Once the amputation is completed, the operative wound is covered with a sterile dressing, the patient is turned again, and the wound is closed. All of our patients regained good health soon after the TLA. Conclusions: Hemicorporectomy can be carried out with good results. Our approach decreases operative time for the second stage of a two-stage TLA and minimizes blood loss.

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Feasibility and Safety of Percutaneous Radiofrequency, Microwave or Cryoablation for Unresectable Thoracic Malignancies in Close Proximity to Heart and Large Vessels C. Pusceddu,[1] L. Melis,[1] A. Fancellu,[2]* M. Melis,[3] G. Meloni.[4] *1. Oncological Hospital of Caglari - Dept. of Radio-oncology, Cagliari, Italy; 2. University of Sassari - Dept. of General Surgery - Clinica Chirurgica, Sassari, Italy; 3. New York University School of Medicine, NY Harbor Healthcare System VAMC, New York, NY; 4. University of Sassari - Dept. of Radiology, Sassari, Italy.*

Background: Close proximity of a tumor to heart or large vessels is considered a relative contraindication to percutaneous ablation. We reviewed our experience with the use of various ablation modalities in such conditions. Methods and Materials: A retrospective review of patients treated at our institution with percutaneous ablation for unresctable lung or mediastinal malignancies (LMM) was performed, and patients with tumors located less than 10 mm from large vessels or pericardium were identified. All ablations were performed under conscious sedation and local anesthesia. The therapeutic outcomes were evaluated by contrast-enhanced CT after 1 month. Immediate and short term results are presented. Results: Between June 2008 to January 2011 we treated with CT-guided percutaneous ablation 27 patients (mean age 64 years) with lesions located within 10 mm from heart or large vessels. Overall, 13 metastases, 12 NSCLC, 1 thymoma, and 1 mesothelial sarcoma were treated with CT-guided radiofrequency ablation (RFA, N=14), microwave ablation (MWA, N=7) and cryoablation (CA, N=6). In all cases, the procedure was technically successful. No intra-procedural arrhythmia occurred. In two patients, an electrode penetrated in the pericardium without consequences. Morbidity consisted of pneumothorax (n=7), and pleural effusions (n=3). At 1-month follow-up, CT revealed complete necrosis in 22 cases and partial (from 70 to 90%) necrosis in the 5 cases. Conclusion: In our experience ablation of LMM in close proximity of hearth or large vessels appears effective and associated with acceptable morbidity. Heat-sink effect did not preclude achievement of complete ablation in the majority of those cases.

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Interleukin-21 for Expansion of T-cells for Adoptive Immunotherapy of Murine Mammary Carcinoma C.K. Zoon,* L. Graham, H.D. Bear. *General Surgery, Virginia Commonwealth University Health System, Richmond, VA.*

Our lab has shown that 4T1 mammary carcinoma tumor-specific lymphocytes activated with bryostatin 1 + ionomycin (B/I) and grown in IL-7/15 far exceeded IL-2 cultured lymphocytes in cell expansion and efficacy against 4T1 flank tumors in vivo. IL-7/15 also shifted the T cells towards a central memory phenotype, previously shown to be more effective at inducing tumor regression. We sought to learn whether IL-21, one of the most recently discovered common gamma chain cytokines, would further improve results. Antigen-sensitized lymphocytes were harvested from BALB/c mice and exposed to B/I. The cells were then cultured in IL-2, IL-21, IL-2/21, IL-7/15 or IL-7/15/21 for 7 or 14 days. Harvested cells were analyzed by flow cytometry and used to treat BALB/c mice previously injected with 4T1 cells four or seven days prior to cyclophosphamide and adoptive immunotherapy. Flank tumors were serially measured. We found that expanding 4T1 tumor-specific lymphocytes in IL-7/15/21 after B/I resulted in increased expansion in vitro vs. cells grown in IL-2 or IL-7/15 (average of 49-fold vs. 5- or 31-fold). Also, IL-21 and IL-2/21 sustained or preferentially expanded a CD44-CD62L+ T cell population (31% and 28% vs. <8%). The combination of IL-7/15/21 increased the percentage of central memory CD8+ T cells (CD44+CD62Lhigh) vs. IL-7/15 (48% vs. 35%), as well as compared to all other groups (<15%). IL-7/15/21 also induced a significant increase in CD8+ cells vs. IL-7/15 (69.8% vs. 54.6%). Moreover, we showed that T cells grown in IL-21 alone or in combination were as or more effective than cells grown in IL-7/15 or IL-2 at curing 4T1 flank tumors, particularly at low treatment doses. We now show that IL-7/15/21 induces greater expansion of lymphocytes in culture, and that cells grown in IL-21, IL-2/21 and IL-7/15/21 are equal or more effective at curing 4T1 flank tumors, particularly at lower cell doses, than cells grown in IL-2. This may have a significant impact on future trials of adoptive immunotherapy. In addition, growing B/I-activated T cells in IL-21 increased a CD44-CD62L+ T cell population, which may eventually prove to be either "naïve-like" T cells, or T "memory stem cells."

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Long-term Pulmonary Function after Metastatectomy for Childhood Osteosarcoma J. Denbo,[2]* L. Zhu,[1] D. Srivastava,[1] D. Stokes,[2] S. Srinivasan,[2] M.M. Hudson,[1] K. Ness,[1] L. Robinson,[1] M. Neel,[1] B. Rao,[1] F. Navid,[1] A.M. Davidoff,[1] D.M. Green.[1] *1. St. Jude Children's Research Hospital, Memphis, TN; 2. University of Tennessee Health Science Center, Memphis, TN.*

Introduction: Complete resection of lung metastases improves survival in patients with metastatic osteosarcoma. Long-term complications can occur following metastatectomy. We evaluated the long-term effect on pulmonary function of metastatectomy in patients treated for osteosarcoma as children. Methods: A review was performed of patients who had previously undergone osteosarcoma pulmonary metastatectomy. Patient, tumor, and treatment variables were collected along with pulmonary function tests (PFTs). PFTs were recorded as a percentage of predicted value and were classified as normal for TLC ≥80%, DLCO ≥75%, FVC ≥80%, and FEV1 ≥80%; test results with a lower percentage were classified as abnormal. Results: Twenty patients had PFTs performed during follow-up. The mean age at diagnosis of osteosarcoma was 12.9 ± 4.6 years. Fifteen patients underwent a single thoracotomy, while 5 patients underwent ≥2 thoracotomies (range 2-5). A total of sixty lesions were resected. Eleven patients had ≤2 lesions resected and 9 patients had >2 lesions (range 3-10) resected. The mean time from the last surgical procedure to measurement of PFTs was 18.0 ± 10.3 years. Approximately one-half of all PFTs were classified as abnormal (TLC 40%, DLCO 42%, FVC 42%, FEV1 50%). Patients with multiple thoracotomies had a higher percentage of abnormal values for TLC, FVC, and FEV1, although because of small numbers these differences did not achieve statistical significance. Thirty-four percent of the PFTs were abnormal in patients who underwent ≤2 resections, while 56% of PFTs were abnormal in patients with >2 lesions resected. The number of resected lesions approached a correlation with abnormal TLC (p=0.09). Six patients received bleomycin, but its use was not associated with abnormal PFTs. No patient received chest radiation therapy. Conclusions: Patients who have undergone pulmonary metastatectomy for osteosarcoma as children often have abnormal PFTs on long-term follow-up. Multiple thoracotomies and increasing number of resected lesions may predict greater impairment of pulmonary function. However, abnormal PFTs can even occur in patients who underwent only a single thoracotomy with only 1 or 2 wedge resections.

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Optimal Management of Malignant Pleural Effusions: VATS with Talc Pleurodesis vs. Tunneled Pleural Catheter M.J. Schuchert,* R. Shah, K.N. McCormick, K. Stewart, A. Pennathur, G. Abbas, O. Awais, D.O. Wilson, J.M. Siegfried, J.D. Luketich, R.J. Landreneau. *Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction Malignant pleural effusions (MPEs) are a marker of advanced or disseminated disease associated with reduced survival (3-12 months). Therapeutic interventions for MPE are palliative in nature, and target the relief of dyspnea and prevention of repeated procedures and hospitalizations secondary to fluid recurrence. In this study, we evaluate efficacy of VATS/Talc Pleurodesis vs. Tunneled Pleural Catheters in preventing re-intervention and re-admission for recurrent MPE. Methods Retrospective review of 234 patients undergoing drainage of malignant pleural effusion via either a VATS with talc pleurodesis (n=117) or insertion of an in-dwelling pleural catheter (n=117). Primary endpoints include recurrence of effusion requiring intervention and hospital re-admissions. Secondary endpoints include length of stay, morbidity, mortality and overall survival. Results Patients undergoing VATS/Talc were younger (66 vs.70 years, p=0.04) and had larger effusions (1,676 vs. 1,214 ml, p=0.002) compared with those undergoing tunneled catheter insertion. Gender distribution (M:F -55:62 vs. 53:64), Charlson Comorbidity Index (10 vs.10), tumor histology, and use of pre-operative chemotherapy (54.2% vs. 55.1%), were similar between respective groups. No significant differences were noted in length of stay, morbidity, recurrence of effusion requiring re-intervention or re-admission [Table]. Pleurodesis permitting tunneled catheter removal was observed in 23.7% of patients. Though in-hospital mortality was equivalent (7.7% vs. 6.8%, p=1.00), VATS/Talc pleurodesis was associated with reduced 30-day mortality (18.8 vs. 36.7%. p=0.003) and better overall survival [Median 6 vs. 2 months, p<0.0001]. Conclusions VATS/Talc pleurodesis and tunneled catheter insertion appear to have equivalent efficacy in preventing re-intervention and re-admission for recurrent MPE. Differences in mortality may be

due to differences in patient age and extent of disease rather than procedure-related morbidity.

Outcomes Following VATS/Talc Pleurodesis vs. Tunneled Catheter Placement

	VATS/Talc (n=117)	Tunneled Catheter (n=117)	P value
Median Length of Stay (days)	5	4	0.27
Morbidity (%)	33.3%	23.9%	0.15
Mortality (%) 30-Day 90-Day	18.8% 39.3%	36.7% 62.4%	0.003 0.0006
Recurrence/Re-Intervention (%)	15.4%	13.7%	0.85
Re-admission (%)	31.6%	26.5%	0.47
Median Survival (months)	6	2	<0.0001

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Utilization of Receptor Targeted Technetium Tc 99m Tilmanocept (Lymphoseek Injection) to Identify and Evaluate the Pathological Status of Sentinel Lymph Nodes vs. Elective Neck Dissection in Patients with Intraoral Squamous Cell Carcinoma: A Preliminary Performance Evaluation Against Technetium Tc 99m Sulfur Colloid in the ACOSOG-Z0360 Study S.Y. Lai,[1]* A. Agrawal,[2] F.J. Civantos.[3] *1. Dept of Head and Neck Surgery, MD Anderson Cancer Center, Houston, TX; 2. The Ohio State University Wexner Medical Center, Columbus, OH; 3. Sylvester Comprehensive Cancer: University of Miami Health System, Miami, FL.*

INTRODUCTION: A phase 3, prospective, multi-institutional, open-label, single arm trial is ongoing to assess the utility and accuracy of Lymphoseek for the intraoperative identification of sentinel lymph nodes (SLNs) in cutaneous and intraoral head and neck squamous cell carcinoma (HNSCC). The results from three clinical sites were pooled for preliminary evaluation against the ACOSOG-Z0360 study in which technetium Tc 99m sulfur colloid (SC) was used. METHODS: Patients were enrolled with a diagnosis of cutaneous or intraoral HNSCC (T1-T4a, N0, and M0). The primary objective was to determine the false negative rate (FNR) associated with Lymphoseek-identified SLNs relative to the pathological status of non-SLNs in the elective neck dissection (END). Only patients with oral cancers, stage T1-T2, N0 from three sites were included in this evaluation. RESULTS: Three enrolling sites provided 16 stage T1 lesions (46%), 19 stage T2 (54%), with 43% (15/35) of patients being positive for pathology after central processing. The median number of SLNs removed per patient with Lymphoseek and SC was four and three respectively. The overall negative predictive values (NPV) for Lymphoseek and SC were 1.00 and 0.96 respectively. Lymphoseek demonstrated that SLN status was highly predictive and consistent with the status of the neck for clinical stage and tumor location with a NPV of 1.00. In comparison, SC exhibited a variable NPV (0.94-1.00) relative to clinical stage and tumor location. Lymphoseek had a 0% FNR overall (zero false negatives of 15 known positives) while SC had a 9.8% FNR.

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Preventing Metastatic Disease by Activating Natural Killer Cells with Perioperative Influenza Vaccination L. Tai,[2] J. Zhang,[2] C. Tanese de Souza,[2] A. Ananth,[2] J.C. Bell,[2] A.P. Makrigiannis,[3] R.C. Auer.[1]* *1. University of Ottawa, Department of Surgery, Ottawa, ON, Canada; 2. Ottawa Hospital Research Institute, Center for Cancer Therapeutics, Ottawa, ON, Canada; 3. University of Ottawa, Biochemistry, Microbiology and Immunology, Ottawa, ON, Canada.*

Rationale: Surgical resection induces Natural killer (NK) cell dysfunction and this has been linked to the development of metastases. We previously demonstrated that preoperative administration of oncolytic viruses can inhibit surgery-induced NK cell dysfunction and prevent metastases. These promising results were met with safety concerns associated with using a live virus immediately prior to surgery. The goal of the current project was to identify attenuated vaccines capable of reversing surgery-induced NK cells dysfunction and attenuating metastatic disease. Methods: Surgical stress was induced by laparotomy and nephrectomy in murine model of experimental (B16 melanoma) and spontaneous (4T1 breast) lung metastases. Vaccinations were administered 24 hours prior to surgery. Mice were euthanized at specific time points and lung metastases were quantified. NK cell activation was measured following surgery and vaccination using in vitro (CD69 cell surface expression, intracellular interferon-γ secretion, and cytotoxicity via 51Cr release) and in vivo (β2-microglobulin negative splenocyte rejection) NK cell assays. Results: Among the panel of vaccines tested (measles-mumps-rubella, diphtheria-polio-tetanus-pertussis-haemophilus, Bacillus Calmette-Guerin, and influenza), influenza was the most potent activator of NK cells. Surgery resulted in significant suppression of NK cells, as measured by in vitro and in vivo assays, but this effect was not seen when influenza was administered preoperatively. Moreover, preoperative influenza vaccination significantly reduced lung metastases in both the experimental B16 and spontaneous 4T1 mouse models as compared to animals that underwent surgery alone. Finally, the efficacy influenza vaccination was significantly reduced following NK cell depletion (α-asialo) suggesting a key role for NK cells in this setting. Conclusion: There are no standard perioperative therapies aimed at preventing postoperative metastases. Attenuated and dead vaccines, such as the influenza vaccine, show promise as neoadjuvant innate immune therapies designed to prevent metastatic recurrence following cancer surgery.

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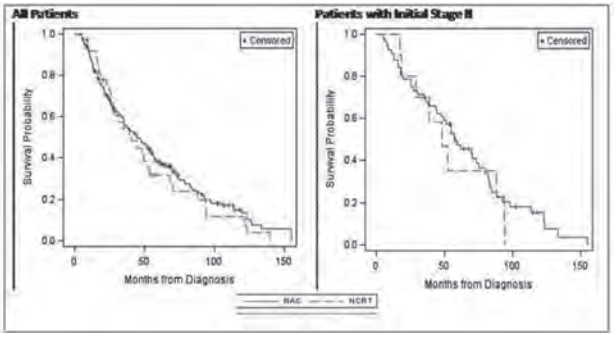
Is Neoadjuvant Chemoradiotherapy Superior to Neoadjuvant Chemotherapy in Resectable Esophageal Adenocarcinoma? A.T. Prescott,[1]* V.P. Koshenkov,[1] T. Koru-Sengul,[1] M.E. Freiser,[1] C. Rosati,[2] J.L. Sparling,[1] B.J. Allan,[1] D. Franceschi,[1] A. Livingstone,[1] E. Avisar.[1] *1. Surgical Oncology, University of Miami, Jackson Memorial Hospital, Miami, FL; 2. University of Pisa, Pisa, Italy.*

Introduction: In esophageal adenocarcinoma (EAC), neoadjuvant therapy offers survival benefits compared to surgery alone, however, little data exists to support the superiority of neoadjuvant chemoradiotherapy (NCRT) over neoadjuvant chemotherapy (NAC). Methods: A retrospective review was performed of all patients with cT2-4NXMX EAC who underwent neoadjuvant therapy and surgical resection at a tertiary referral center from 2000 to 2012. Patients were stratified by NCRT or NAC. Patient and tumor characteristics, procedure, complications and survival rates were compared. Differences in proportions were tested by chi-squared test. Survival rates were estimated using Kaplan-Meier method. Results: 237 patients met inclusion criteria; 199 (84%) received NAC, 38 (16%) received NCRT. The two groups were comparable in age, sex, tumor grade, clinical stage, type of surgery, R0 resection rate, and length of stay. Tumor location in the NAC group was 97% distal/GEJ vs. 87% in NCRT (p=0.018). The NCRT group had higher response rates to neoadjuvant therapy (68 % vs. 45%, p=0.012). The NAC group had more overall complications (45.2% vs. 42.1%), pulmonary complications (15.1% vs. 53%), anastomotic leaks (17.1% vs. 13.2%), and infections (10.6% vs. 7.9%), without statistical significance. The NCRT group had more cardiac complications (18.4% vs. 7%), which trended towards statistical significance (p=0.054). Although not statistically significant, the NCRT group had higher perioperative mortality (7.9% vs. 3.5%). When comparing all stages of NAC vs. NCRT, median survival (45 vs. 41 months, p=0.47), 3 yr (56% vs. 54%) and 5 yr (38% vs. 32%) survivals were comparable. In stage II, patients treated with NAC had better median survival (57 vs. 48 months, p=0.49) and higher 5 yr survival rates (47% vs. 35%). Conclusion: NAC and NCRT followed by surgical resection offer equivalent rates of R0 resection, length of stay, and overall survival. Although patients treated with NCRT had better response rates, this group had higher rate of cardiac complications and perioperative mortality. Stage II patients treated with NAC seem to have an improved median and 5 yr survival.



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Second Cytoreductive Surgery and HIPEC for Peritoneal Surface Malignancy and Peritoneal Carcinomatosis: A Single Institution's Experience J. Wong,* M. Teo, G. Tan, C. Tham, K. Soo. *National Cancer Centre Singapore, Singapore, Singapore.*

Introduction Peritoneal carcinomatosis carries a poor prognosis with limited survival of only 6 months on diagnosis. Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) have been shown to be effective in selected patients with favourable histological subtypes. Recurrence after CRS and HIPEC poses a management dilemma but a repeat CRS and HIPEC may confer improved survival in a selected group of patients. Material and Methods 104 patients underwent CRS and HIPEC for peritoneal carcinomatosis and peritoneal surface malignancy from Jan 1991 to Oct 2012. 17 patients had recurrence in the peritoneum only of which three underwent a second CRS and HIPEC. A retrospective analysis of the clinical and prognostic factors was performed. Results There were 2 females and 1 male who underwent a second CRS and HIPEC. The primary malignancies were as follows: 2 cases of appendiceal cancer and 1 case of peritoneal mesothelioma. The mean follow-up period was 2.4 years (range 0.6 – 7.4 years). The mean Disease free interval (DFI) was 36.25 months (range 24 - 87) and mean Disease Free Survival was 29 months (range 7-89). The mean overall survival was also 29 months. To date, all the patients are still alive and well post second CRS and HIPEC. Conclusion This retrospective analysis of the patients in our institution who have undergone a second CRS and HIPEC provides evidence that this aggressive mode of treatment confers prolonged DRS and OS in a selected group of patients.

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The Sphingolipid Transporter Spns2 Maintains Levels of Sphingosine-1-Phosphate in the Lymphatic System and Regulates Lymphatic Vessel Networks M. Nagahashi,* E.Y. Kim, A. Yamada, S. Ramachandran, J.C. Allegood, N.C. Hait, M. Maceyka, S. Milstein, S. Spiegel, K. Takabe. *Virginia Commonwealth University, Richmond, VA.*

Background. Sphingosine-1-phosphate (S1P), a ligand for five specific receptors, is a potent lipid mediator that plays important roles in cancer progression, lymphocyte trafficking, and immune responses. We recently reported that S1P secreted by breast cancer cells promotes their progression by stimulating angiogenesis and lymphangiogenesis. S1P is produced inside cells and therefore must be secreted in order to exert its effects through these receptors. Spinster 2 (Spns2) is one of the cell surface transporters thought to secrete S1P. Although lymphatic endothelial cells contribute to regulation of S1P levels in lymph, little is known how S1P levels are maintained in the lymphatic system. Methods. Spinster 2 knockout mice (Spns2tm1a(KOMP)Wtsi) were used, and the lymphatic system was examined by flow cytometry and immunofluorescent staining. Sphingolipids in the blood, lymph, and organs were determined by liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS). Results. We confirmed that Spns2 can export endogenous S1P from cells and also dihydro-S1P, which is active at all cell surface S1P receptors. Moreover, Spns2-/- mice have decreased levels of both of these phosphorylated sphingoid bases in blood, accompanied by increases in very long chain ceramide species, and have defective lymphocyte trafficking. Surprisingly, levels of S1P and dihydro-S1P were increased in lymph from Spns2-/- mice as well as in specific tissues, including lymph nodes, and interstitial fluid. Moreover, lymph nodes from Spns2-/- mice have aberrant lymphatic sinuses, which appear collapsed, with reduced numbers of lymphocytes. Conclusions. Our data suggest that Spns2 is an S1P transporter in vivo that plays a role in regulation not only of blood S1P but also lymph node and lymph S1P levels and consequently influences lymphocyte trafficking and lymphatic vessel network organization. M.N. is a Japan Society for the Promotion of Science Postdoctoral Fellow. S.S. is supported by NIH R37GM043880, and K.T. by NIH R01CA160688 and Susan G. Komen for the Cure Investigator Initiated Research Grant.

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Development of a Robotic Thoracic Surgery Program in a Comprehensive Cancer Center P. Ross,* P. Skabla, E. Kassis, V. Daniel, K. Glass, J.L. Wilson. *Thoracic Surgery, Ohio State University, Columbus, OH.*

Minimally invasive thoracic resections may have multiple advantages for patients including reduced pain, shortened hospitalization, and earlier return to daily activity. Oncologic outcomes may be improved and patients are more likely to complete adjuvant therapy. However, this approach has not been widely accepted; the majority of lobectomies are still performed as thoracotomy approach. We have evaluated robotic-assisted thoracic surgery (RATS) as a platform for achieving a greater percentage of minimally invasive procedures. Since September 2011, we have performed 100 RATS procedures including lobectomy and bilobectomy (61), mediastinal resections (14), and sublobar pulmonary resection with lymphadenectomy (19). Resections included stages I-IIIa; stage IIIa patients included those receiving induction therapy. The mean age is 61.5 years (21-84); there were 56 females and 44 males. Mortality rate was 1%; patient died 30 days post op from an MI. Seven planned robotic cases were converted to open; reasons include bleeding (1), inadequate single lung ventilation (2), granulomatous nodes (2), failure to progress (2). We assessed lobectomy outcomes by quartile. There were 5 conversions to open thoracotomy in the first quartile and 0 conversions in the last. Procedure time was reduced from 276.1 to 216.4 minutes. Length of stay decreased from 7 days to 5 days. Development of a robotic program included training a multi disciplinary team within the operating room. Our results document performance improvement as expertise is acquired. The robotic platform has been extended to patients for whom thoracoscopy would not have been considered. Robotic-assisted surgery is safe and increasingly requested by patients interested in minimally invasive approach. This technique should be part of a comprehensive thoracic oncology program.

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Melphalan: A Promising Agent in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) A. Sardi,* V. Gushchin, C. Nieroda, M. Sittig, S. Shankar, J. Francis, R. MacDonald, P. Ledakis. *Mercy Medical Center, Baltimore, MD.*

Introduction: CRS/HIPEC is a treatment option for malignancies with peritoneal dissemination. Frequently, patients have undergone and failed multiple systemic chemotherapies and previous surgeries including CRS/HIPECs. The first line agents for HIPEC have been Mitomycin-C or a platinum based regimen. We have used Melphalan as the agent of choice in patients with recurrences following failed therapies. Methods: A retrospective review of a prospective database of 247 patients revealed a total of 25 patients who received intraoperative intraperitoneal melphalan (50mg/m2) during 31 CRS/HIPEC procedures. Of these, 19 were repeat surgeries. Diagnoses included 17 appendiceal, 1 colorectal, 2 ovarian, 2 uterine sarcomas, 2 primary peritoneal, and 1 mesenteric sarcoma. Thirty-six percent were male and 64% female. Results: Postoperative leukopenia occurred in 52% of patients receiving melphalan. Filgrastim was administered to 36% for leukopenia during postoperative days 7-14. Sixteen percent of patients received filgrastim as prophylaxis during postoperative days 1-3. The remaining 12 patients did not require intervention. The PCI score was >20 in 76% of patients (19/25). Complete cytoreduction (CC-0/CC-1) was obtained in 88% (22/25). Seventeen patients are alive and 7 deceased. Overall survival rate is 63.6% (17/25). The 1, 3, 5, and 10 year survival rates since diagnosis are 95.8%, 84.5%, 50.9%, and 38.2%, respectively. The survival rate since administration of melphalan at HIPEC is 89.4% at 1, 45% at 3, and 30% at 5 years. The use of Melphalan with appendix cancer has a 1, 3 and 5 year overall survival rate of 91.7%, 48.1%, and 32.1%, respectively. Conclusion: In spite of the myelosuppressive effect of melphalan, survival statistics support its use as an effective alternative agent in patients undergoing CRS/ HIPEC following previously failed therapies.

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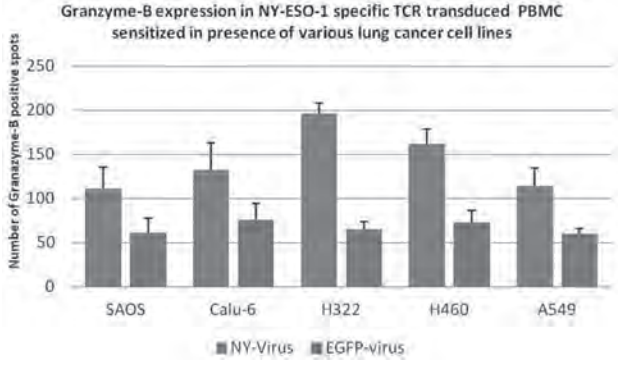
Transfection of Naïve T Cells with a T Cell Receptor Specific for NY-ESO Cancer Testis Antigen Enhances the T Cell Response Against NY-ESO+ Lung Cancer Cell Lines N.N. Gangopadhyay, A. DeLeo, A. Opest, R.J. Landreneau, J.D. Luketich, M.J. Schuchert.* *Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction Cancer testis antigens (CTA) have been shown to generate both humoral and cellular antigenic responses in cancer patients. Recent data utilizing immunological adjuvants with CTA, as well as the development of vectors to achieve transgenic expression of T cell receptors (TCRs) against CTA in patients with melanoma, have demonstrated tumor responses against

melanoma in vitro and in animal models. In the current study, we seek to characterize a model of T cell immunotherapy based on transgenic expression of T cell receptors with specificity against the NY-ESO CTA in the setting of lung cancer. Methods A bicistronic retrovirus vector carrying NY-ESO-1 specific TCRα and TCRβ chains was kindly provided by Steven A. Rosenberg M.D., Surgery Branch, National Cancer Institute, National Institutes of Health. We were able to successfully generate this retrovirus vector within a GP293 packaging cell line. Jurkat cells and naïve human PBMC-derived T cells were transduced with a TCR specific for NY-ESO-1 utilizing this retrovirus construct. This transduced receptor is capable of recognizing NY-ESO-1 antigen in the context of HLA-A2. Results Jurkat cells transduced with TCR against HLA-A2 specific NY-ESO-1 antigen showed modest release of IFNγ in lung NY-ESO+/HLA-A2+ cancer cell lines 201T (6-fold increase) and H322 (2-fold increase) as detected by the ELISPOT assay. In comparison to the T cells transduced with a control virus carrying EGFP, T cells expressing NY-ESO-1 specific TCR released a significantly higher amount of Granzyme B when cultured with lung cancer cell lines expressing NY-ESO [Figure]. Conclusions Naïve T cells that are transfected with TCR specific for NY-ESO-1 are capable of responding to lung cancer cell lines expressing this CTA. These results will need to be further validated by assessing tumor kill in vitro and in animal models.



P234

Microfabricated Polymeric Vessel Mimetics for Oxygenation of 3-D Cancer Cell Cultures C. Das,* A. Jaeger, T. Pohida, N. Morgan, M. Gottesman. *NIH, Bethesda, MD.*

Background: Modeling tumor growth in vitro is often necessary for cost-effective testing of hypotheses in preclinical cancer research. 3-D cell culture is widely thought to offer an improvement over monolayer culture for studying cellular processes in cancer biology because of the preservation of cell-cell and cell-ECM interactions which impact cellular phenotype. However oxygen transport poses a major barrier to mimicking in vivo environments. We hypothesized that we can better mimic the in vivo enviroment using a novel system for controlling gas exchange in cancer cell cultures using silicone hydrogel synthetic vessels. Methods: Polydimethylsiloxane (PDMS) molds were manufactured by creating positive masters of an array of pillars with geometries similar to blood vessels. We spun high viscosity SU-8 epoxy photoresist onto silicon wafers and exposed to filtered UV, which were developed. PDMS negatives were manufactured using the positives as templates. Silicone hydrogel was cast into the negative PDMS molds. These membranes were inserted into a bioreactor and surrounded by basement membrane extracts upon which fluorescent Ovcar8 cells were cultured. Cultures were imaged utilizing confocal microscopy. RNA was extracted from cultures and qRT-PCR was performed. Data were analyzed using Significance Analysis for Microarrays. Results: Mean cell cluster size in BME without oxygen diffusing hydrogels was 50μm whereas with synthetic vessels, the mean cell cluster size was 183μm, p=0.01. In addition to size differences, we showed oxygen tension gradients inside the clusters oxygenated by synthetic vessels had a 100μm drop-off to anoxia, which is consistent with in vivo studies. We also showed differential gene expression in our study. Conclusions: Our study demonstrates differing growth patterns and altered gene expression associated with modifying gas distribution to better mimic in vivo conditions. Further studies will be conducted to extend this system into a drug discovery platform. If successful, it could serve as a cost effective intermediate for drug screening between traditional in vitro culture systems and costly animal models.

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Malignant Cutaneous Adnexal Tumors Do not Require Routine Sentinel Lymph Node Biopsy M.A. Barnes,* A. Hestley, D.R. Murray, M. Rizzo, G.W. Carlson, D.C. Parker, K.A. Delman. *Surgical Oncology, Emory University School of Medicine, Atlanta, GA.*

Introduction: Malignant cutaneous adnexal tumors (MCATs) are rare neoplasms that do not have a well-studied treatment algorithm. They are generally treated by excision alone. Given its successful application in other cutaneous malignancies, sentinel lymph node biopsy (SLNB) has been advocated by some for use in MCATs. The data supporting this is limited and this study represents a single-institution experience with these lesions to help characterize their risk of nodal metastases. Methods: A retrospective chart review was performed. Clinicopathological factors, recurrence patterns and long-term follow up were documented. Survival analysis was performed. Results: Forty-eight subjects were identified. Mean age was 69 years with locations including the face (36%), extremities (24%), periocular sites (16%), trunk (12%), scalp (8%), and other head and neck sites (4%). Histologic distribution was sebaceous carcinoma (56%), porocarcinoma (17%), eccrine carcinoma (13%), adenocarcinoma (10%), and hidradenocarcinoma (4%). Median follow-up was 3.2 years (range 1-17 years). Nine subjects (18.8%) recurred locally, and recurrence was inversely associated with age (p=0.04). Four (8.3%) demonstrated lymph node involvement, none without first developing local recurrence. 5-year disease-specific survival was 97% (CI 81.4-99.6%). Conclusion: This study, one of the largest reported analyses of MCATs, is still limited by the small number of subjects. MCATs seemingly develop nodal recurrence only after demonstrating aggressive local biology. SLNB may best be applied selectively, possibly only in patients with local recurrence.

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Induction Therapy Followed by Surgery for Non-Small Cell Lung Cancer (NSCLC) in a Community Cancer Center B.G. Dalton,* R.B. Hird, R.K. Orr, C.L. Nguyen. *Spartanburg Regional Medical Center-Gibbs Cancer Center, Spartanburg, SC.*

Introduction: Neoadjuvant therapy followed by definitive surgical resection remains controversial for NSCLC. The purpose of this study is to review our immediate surgical outcomes for these patients, as well as to investigate survival trends. Methods: A retrospective review of all consecutive pulmonary resections for NSCLC from October 2006 to April 2012 was performed. Of the 272 patients, 28 (10.3%) of them received induction chemotherapy or chemoradiation. Mean follow up was 32 months from time of resection. Two patients were lost to follow up. Operative data were reviewed and survival rates calculated. Results: Clinical staging (cStage) groups included IIb (18%), IIIA (75%) and IV (7%). Concurrent chemoradiation was utilized in 23/28 patients (82.1%) vs. 5/28 (17.9%) patients received chemotherapy alone. Of the cStage IIIA patients, 17 of 21 (81%) were given chemoradiation and 4 were given chemotherapy alone. At the time of resection, a thoracotomy was used in 25/28 patients (89%) and a thoracoscopic approach in 3/28 patients (11%). Twenty of 28 patients (71%) had a lobectomy performed, 7 patients (25%) were treated with a pneumonectomy and 1 patient had a bilobectomy. Overall complication rate was 25%. Overall 30-day mortality was 7.1% (2/28); 0% (0/20) for lobectomy patients and 14.2% (1/7) for pneumonectomy patients. Pathological downstaging (PD) occurred in 22 of 28 patients (79%). A complete pathologic response (pCR) was seen in 9 of 28 patients (32%); 7/9 (77.8%) received chemoradiation and 2/9 (22.2%) received only chemotherapy (p<0.05). Overall survival (OS) was improved in every cStage group receiving induction therapy. For the cStage IIIA group, OS rate at 1 and 2 years was 82.3% and 71.4%, respectively and disease-free survival rate at 1 and 2 years was 64.7% and 57.1%, respectively. Conclusion: Our data demonstrates that induction therapy followed by resection of NSCLC is safe and results in PD in most patients. Furthermore, the use of chemoradiation is more likely to result in pCR than the use of chemotherapy alone. Early survival trends for these patients match more closely their final pathological stage than their original cStage.

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Preserving Fertility in Young Cancer Patients Using Biomaterials in a Murine Model of Infertility A. Hardy,[1]* E. Kniazeva,[3] L.D. Shea,[3] J.S. Jeruss.[2] *1. Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL; 2. Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; 3. Northwestern University Department of Chemical and Biological Engineering, Evanston, IL.*

Introduction: For premenopausal oncology patients, the gonadotoxic effects of chemotherapy and radiation may result in premature ovarian failure. Although there has been some success in restoring ovarian function with the autotransplantation of cryopreserved ovarian tissue, concern exists about reintroducing latent malignant cells and inducing relapse. We examined the potential for transplanting isolated primordial follicles using biomaterials to provide the mechanical support necessary to facilitate follicle development. Methods: Ovaries from 6 day old C57BL/6j x CBA/Ca female mice underwent chemical and mechanical digestion. Primordial follicles were retrieved, incorporated into biomaterials, and made into beads comprised of either fibrin alone or a combination of fibrin with alginate or collagen. Beads were transplanted into the empty bursae of adult isogenic female mice after ovariectomy. After 3 days, mice were sacrificed and the beads retrieved for cryosectioning and histological staining. Results: Control whole ovaries, which have a predominance of primordial and primary follicles, survived and demonstrated evidence of activation. At the time of sacrifice, pre-antral and antral follicles encompassed the majority of the follicle pool. For the transplanted follicle groups, follicles encapsulated within fibrin alone demonstrated greater survival compared to those embedded within fibrin combined with alginate or collagen. Additionally, the fibrin alone group showed the greatest amount of activation from primordial to primary follicles. Conclusions: Our work demonstrates the ability to successfully transplant isolated primordial follicles in vivo and shows survival and activation for up to 3 days post-surgery using biomaterials. This work also suggests that use of fibrin alone may be more conducive to healthy follicle development in this model. Future work will focus on optimization of the study biomaterials to facilitate follicle survival at later time points with the goal of providing young female cancer patients with safe options for fertility preservation.

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Survival Analysis of 16 Cases of Head and Neck Synovial Sarcomas in Mexico Compared with Extremity Synovial Sarcomas R.A. Salcedo-Hernandez,* L.S. Lino-silva, K. Luna-Ortiz, H. Martínez-Said, . Herrera-Gómez. *Surgical Oncology, Instututo Nacional de Cancerología de México, Mexico, mexico, Mexico.*

Introduction. We analyze Synovial Sarcoma (SS) of the head and neck in the period from 1980 to 2010 for identification of characteristics associated with survival improvement and compare it with the survival of Extremity SS. Method. The authors reviewed clinical records and histopathologic material with molecular analysis for SYT/SSX gene rearrangement of 16 patients to analyze clincopathologic characteristics and their association with survival and compare survival with 174 extremity SS. Results: The average age was 41.6 years (range 23-86). Eight cases occurred in males (50%) and 8 in women. The most prevalent site of presentation was the parapharyngeal space. The mean tumor size was 5.38 cm; in seven cases (56.2%) was < 5 cm. Sixty-nine percent occurred in Stages II-III and 9% in stage IV. Fifteen cases were excised, with R0 resection in 7 (46.7%) and R1 resection in 8 (53.3%). No patients with R0 resection recurred whereas three patients with R1 resection (43%) did ($p = 0.035$). Only patients with R0 surgery had better survival than those who received another treatment ($p = 0.045$). SS of head and neck shows 5-year overall survival of 58% vs 44.6% of cases with extremity SS ($p=0.450$). Conclusion. We present the results of one series of SS of the head and neck where the most prevalent site of presentation is pharapharyngeal space. Surgical resection with clear margins correlates with low recurrence. Head and Neck SS has similar survival rates respect extremity SS.

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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Recurrent Ovarian Cancer – An Asian Experience C.S. Chia,* G. Tan, C. Tham, K. Soo, M. Teo. *National Cancer Centre Singapore, Singapore, Singapore.*

Title: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy(HIPEC) for recurrent ovarian cancer – An Asian experience. Background: More than 70% of patients with epithelial ovarian cancer present at a late stage, with many of them having evidence of peritoneal disease. Cytoreductive surgery is the mainstay of treatment for primary ovarian cancers. Median survival after recurrent ovarian cancer is 12-18months with a 5 year overall survival of less than 10%. The combination of cytoreductive surgery and HIPEC has been used as a local aggressive therapy in primary and recurrent ovarian cancers to improve survival in this set of patients. This study reviews our 7 years experience with this procedure in our Asian population of patients with recurrent ovarian cancers. Methods: During the period from March 2005 to July 2012, 39 patients underwent cytoreductive surgery and HIPEC for ovarian cancer. Data was obtained from case records and a retrospective analysis was carried out. Results: Mean age of the patients was 49.7years(range 23-68). Mean time to recurrence was 36 months(range 2-142months). Average PCI(peritoneal cancer index) score was 13(range 2-31). Median operative time was 480minutes. Median length of stay was 17days. 30 day mortality was 0%. Minor complication rate was 28.2% and major complication rate was 38.5%. Median disease free survival was 16.9 months. Our 1, 3 and 5 year disease free survival rates were 63.3%, 22.6% and 11.3%. Our 1, 3 and 5 year overall survival rates were 93.6%, 55.4% and 55.4% respectively. Conclusion: Cytoreductive surgery and HIPEC is a safe procedure with low mortality and acceptable morbidity rate. The procedure has also shown to improve overall survival rates. It should be considered an option for patients with recurrent peritoneal disease from epithelial ovarian surgery.

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Development of Palliative Care Index: Opportunities for Assessment of Palliative Outcomes for Surgery in Advanced Malignancy S. Kwon,* J. Park, D.R. Byrd, D. Flum. *General Surgery, University of Washington, Seattle, WA.*

Introduction Wide variation of healthcare utilization in patients with advanced malignancy has been suggested yet studies looking at quality of end-of-life care and palliative outcome measures are limited. Methods We developed a metric, Palliative Care Index (PCI), that measures the total number of hospitalization and emergency room visit days from diagnosis divided by the number of survival days from diagnosis then multiplied by 100. Retrospective analysis was performed looking at PCI using the linked Surveillance, Epidemiology and End Results (SEER) Medicare database (1996-2007) in patients ≥66 years with stage IV colorectal cancer with at least 6 months of survival. We calculated the PCI for those undergoing surgical interventions (versus non-surgical treatment) for diagnosis of bowel obstruction, gastrointestinal bleeding, and perforation. Results 4,355 patients were evaluated in this window of potential palliation with an overall mean PCI of 8.8 (SD ± 11.9). There was a significant variation of PCI between SEER registries from 3.9 (SD ± 6.3) to 12.9 (SD ± 14.6) ($p<0.01$). PCI was significantly higher for those who were younger, with higher comorbidity indices, lived in big metropolitan areas, and were African Americans. Among those with hospital admission for bowel obstruction (n=664), patients undergoing surgical intervention in their initial presentation (n=336, 50.6%) had a significantly lower PCI (13.1 ± 9.1 surgery vs. 18.8 ± 21.8 no surgery, $p<0.01$). Similar difference in PCI was noted for those with perforation [15.3 ± 13.1 surgery (n=67) vs. 33.8 ± 28.6 no surgery (n=11), $p<0.01$]. Opposite finding was observed for those admitted with gastrointestinal bleeding [15.6 ± 12.2 surgery (n=126) vs. 12.2 ± 16.1 no surgery (n=326), $p=0.02$]. The adjusted Cox proportional hazards model demonstrated similar findings. Conclusions Outcome measures that focus on degree of palliation are difficult to develop using administrative database but can be useful in objectively exploring the utility of certain interventions in care of patients with advanced malignancy.

Cox proportional hazards model comparing surgical intervention and non-surgical intervention, and their impact on Palliative Care Index (PCI) for stage IV colorectal cancer patients with survival of at least 6 months who were admitted to the hospital for obstruction, perforation, or bleeding. The PCI was defined as binary variable (set at top quartile PCI value for each diagnosis - 18 for bowel obstruction, 16 for gastrointestinal bleeding, and 19 for perforation).

	Bowel Obstruction	Perforation	Gastrointestinal Bleeding
Surgical Intervention Performed	0.5 (0.4-0.7)	0.5 (0.2-1.7)	1.7 (1.1-2.5)
Age	1.1 (1.0-1.3)	1.0 (0.7-1.5)	1.2 (1.1-1.4)
Sex	1.1 (0.8-1.5)	0.3 (0.1-0.9)	1.0 (0.7-1.4)
Charlson's Comorbidity Index	1.0 (0.9-1.2)	0.7 (0.3-1.8)	1.2 (0.9-1.5)
Race	1.1 (0.9-1.5)	1.6 (0.6-4.2)	0.9 (0.6-1.3)
SEER Registry	1.0 (0.9-1.0)	1.0 (0.9-1.0)	0.8 (0.6-1.1)
Residence	1.0 (0.9-1.0)	0.7 (0.4-1.4)	0.8 (0.6-1.1)

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Isolated Chemotherapeutic Perfusion as Neoadjuvant Therapy for Advanced/Unresectable Pelvic Malignancy H. Wanebo,[1]* J. Belliveau,[1] G. Begossi,[2] E. Gustafson.[1] *1. Landmark Medical Center, Woonsocket, RI; 2. Alta Bates Summit Medical Center, Oakland, CA.*

Introduction: Previous chemo radiation (CRT) usually precludes neoadjuvant therapy for advanced pelvic malignancy. Isolated pelvic perfusion (IPP) provides high tissue drug levels, less toxicity than systemic therapy and may enhance resectability of advanced pelvic malignancy. We have done 113 IPP in 75 patients (pts), 59 pre operative and 16 palliative. Methods: 50 pts had advanced irradiated rectal recurrence (34 pre-op and 16 palliative), 8 pts had advanced anal squamous cancer (SCC), 6 pts had pelvic sarcoma; 4 pts had pelvic/perineal melanoma (MEL), and there were 5 advanced GYN cancers, and 2 bladder cancer (BC) pts. IPP was done using regimens targeted to malignancy type. High dose IPP with stem cell support was done in 3 advanced chemo resistant pts. Results: Neoadjuvant IPP in 26 recurrent rectal cancer pts rendered 15 resectable with acomplete path CR in 2 patients, facilitating curative pelvic resection in 7 pts. The remaining 8 pts were non-resected because of disease, medical status (5 pts), or pt refusal (3 pts). Median overall survivall (OS) post IPP was 24 mos in 15 resectable pts, 30 mos in the 7 resected pts (2 survived > 5 yrs) and 8 mos in 11 non-resectable pts. It was 23/8 (resected/non resected) months in 8 advanced SCC anal pts and 28/24 mo in advanced gyn cancer pts (endometrial/ovarian) and 13 mos in 4 advanced melanoma pts and was only 5 mos in 6 sarcoma pts (only 1 resectable). High dose IPP with stem cell support induced significant regression (with resection) in 2 of 3 pts with advanced chemo resistant (Endometrial/Melanoma) malignancy. Overall of 59 neoadjuvant pts, 34 (58%) responded to IPP, 21 (36%) were resected, and the remaining 25 pts (42%) were considered reasonably palliated. Conclusion: IPP has promise in augmenting resectability (or palliating) selected patients with advanced pelvic malignancy not amenable to conventional chemo RT. IPP responsive tumors included recurrent rectal cancer, anorectal cancer,localized gyn cancers and melanoma, whereas sarcomas were quite resistant. Biologic therapy or stem cell support are viable future options to enhance outcome of IPP.

P243

Risk-adjusted Learning Curve for Peritoneal Cytoreductive Surgery: The Effect of Mentoring and System Learning on Postoperative Complications Y.J. McConnell,* L.A. Mack, S. Sun, W.J. Temple. *Division of Surgical Oncology, University of Calgary, Calgary, AB, Canada.*

Purpose: The initial learning curve for peritoneal cytoreductive surgery (CRS) is lengthy. The goals of this study were to (1) develop a real-time quality monitoring tool for complications following CRS, and (2) use this tool to explore the effect of mentoring and system experience on the learning curve. Methods: A prospective database of patients undergoing CRS was used to test the cumulative summation (CUSUM) control chart method of monitoring major complications (Dindo-Clavien grade III/IV/V) over time. It was tested in 2 cohorts of patients – those of a senior surgeon (SS) starting a new CRS program, and those of a junior, mentored, surgeon (JS) in an established CRS program. Two risk-adjustment models were tested – one used retrospective internal logistic regression (IRL) within the SS cohort, the second used a summary score of resections (peritoneal resection index, PRI). Results: The two cohorts comprised 183 and 97 patients. The IRL model predicted the risk of complications well in the SS cohort (Hosmer-Lemeshow (HL) test 4.50, p=0.609) but not in the JS cohort (HL 22.37, p=0.001). The PRI model better predicted this risk in both cohorts (SS: HL 3.53, p=0.896; JS: HL 5.43, p=0.608). The PRI-adjusted CUSUM function demonstrated a shortened initial learning curve (65-75 vs. 90-130 cases) for the JS compared to the SS. If used prospectively, this model would have signaled after 2-4 sequential major complications in low risk patients, and triggered >10 evaluations of surgeon/system performance over the cases studied. After the initial learning curve, the non-risk-adjusted CUSUM rose as more complex patients underwent surgery. The PRI model adjusted for this changing patient mix and its CUSUM continued to accurately detect short runs of complications that would warrant investigation of technical and systemic factors. Conclusion: With mentoring and system level experience, the learning curve for CRS can be shortened. Implemented prospectively, a PRI-adjusted CUSUM function could provide real-time quality monitoring and contribute to earlier improvements in surgeon and system factors.

Cumulative summation (CUSUM) control charts for major complications following peritoneal cytoreductive surgery in senior and junior surgeon cohorts. Upper graphs: non-risk-adjusted CUSUM functions. Lower graphs: risk-adjusted CUSUM functions using peritoneal resection index (PRI) for risk prediction.

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Breast and Prostate Cancer Survivor-Reported Comorbidities in a Survivorship Clinic S. Misra,* T. Lay, A. Poirier. *Surgical oncology, Cancer Treatment Centers of America, Zion, IL.*

Introduction: Post-treatment follow-up and management of late/long-term morbidities has been an issue with cancer survivors. This study reviews prostate and breast cancer survivors' self-reported complaints during calendar year 2011 at a regional cancer center. Methods: Survivorship patients (n=380) completed a self-assessment during calendar year 2011; 114 were prostate cancer survivors, 110 were breast cancer survivors. The definition of survivorship patients is definitive treatment is complete; no evidence of disease and post 2 surveillance visits without change in status – patients receiving maintenance/hormone therapy accepted. Patients complete a survivorship symptom inventory instrument using a 0-10 Likert scale. Incidence, intensity and a composite of incidence and intensity (relevance) were tabulated. Results: Self assessments of 224 breast and prostate cancer patients were reviewed with emphasis on high incidence and high frequency issues. Conclusions: For prostate cancer survivors the three highest relevance issues are: sexuality, disrupted sleep patterns and fatigue. The three highest relevance issues for breast patients are disrupted sleep patterns, fatigue and anxiety/depression. More research is needed in understanding and treating these issues and improving cancer survivors' overall quality of life. Patients with prostate cancer.

Prostate Cancer	Pain	Fatigue	Sleep	Numbness	Dyspnea	Memory	Mouth	Sexuality	Bowels	Weight	Swelling	Depression	Relationships
Avg. reported score	2.25	3.21	3.32	1.71	1	2.24	1.41	5.36	2.2	1.87	0.75	2.28	1.69
No. reporting issue	55	92	79	52	31	82	43	96	63	58	25	72	50
Avg. intensity of those reporting	4.67	3.98	4.8	3.75	3.68	3.11	3.74	6.36	3.98	3.67	3.4	3.61	3.86
Reporting issue %	48.3	80.7	69.3	45.6	27.2	71.9	37.7	84.2	55.3	50.9	21.9	63.2	43.9
Breast Cancer													
Avg. score	2.99	3.55	3.69	2.5	1.25	3.33	1.19	2.57	1.4	2.52	1.51	3.33	1.58
No. reporting issue	67	92	83	66	46	91	38	54	41	66	39	85	40
Avg. intensity of those reporting	4.91	4.25	4.89	4.17	3	4.02	3.45	5.24	3.76	4.2	4.26	4.31	4.35
Reporting issue %	60.9	83.6	75.4	60	41.8	82.7	34.5	49.1	37.3	60	35.5	77.3	36.4

P245

Is Surveillance Imaging Effective for Detecting Treatable Recurrences in Melanoma Patients? N.M. Rueth,* Y. Xing, Y. Chiang, M.I. Ross, J. Gershenwald, J.E. Lee, R.E. Royal, A. Lucci, J. Cormier. *The University of Texas MD Anderson Cancer Center, Houston, TX.*

INTRODUCTION: NCCN guidelines for surveillance of patients with melanoma are largely consensus- rather than evidence-based, resulting in sig-

nificant practice variation. To help guide resource utilization, we aim to identify the effectiveness of surveillance imaging for detecting melanoma recurrences that may be treated with curative intent. METHODS: Using diagnostic test characteristics from a meta-analysis and transition probabilities from patient level data, a Markov model was created to simulate the natural history of patients with resected stage I-III melanoma. As a base estimate, imaging was assumed to detect regional and distant recurrences (R/DR) of which 80% and 20% were surgically treatable, respectively. We calculated stage-specific 5-year R/DR per 10,000 patients undergoing CT or PET/CT scans at 6- or 12-month intervals. The positive (PPV) and negative predictive values (NPV) and associated change in life expectancy were calculated and compared to clinical exam (CE) alone. RESULTS: CT or PET/CT at 6-month intervals detected treatable R/DR in 6.4% of stage I, 18.5% of stage II, and 33.1% of stage III patients. 12-month imaging intervals decreased the detection of treatable R/DR to 3.0%, 7.9%, and 13.0%, respectively. Interpreting model results for 12-month PET/CT surveillance in stage IIIC patients, 26 PET/CT scans were needed to detect 1 treatable recurrence; 250 PET/CT scans were needed per recurrence in stage I. The high false positive rate of CT (20%) and PET/CT (10%) resulted in low PPVs, particularly for stage I patients (Table 1). Both CT and PET/CT were effective at predicting absence of disease. Neither imaging modality nor time interval strategy resulted in a gain of more than 2 months average life expectancy. CONCLUSIONS: The effectiveness of surveillance imaging for detecting treatable melanoma recurrences is limited. Even in stage IIIC patients with higher recurrence rates and better PPV, minimal gains in life expectancy were noted. The benefits of surveillance imaging should be examined in the context of risk and cost. These data support the NCCN guidelines for stage I and II melanoma, but challenge the recommendations for stage III disease.

Table 1: Predictive value and clinical impact of surveillance imaging strategies

		6-month interval			12-month interval		
		PPV (%)	NPV (%)	Average increase in life expectancy (months)	PPV (%)	NPV (%)	Average increase in life expectancy (months)
Stage I							
	CE + CT	1.5	99.8	0.3	1.4	100	0.2
	CE + PET/CT	4.5	99.9	0.4	5.0	99.9	0.2
Stage II							
	CE + CT	4.6	99.2	0.9	4.5	99.2	0.5
	CE + PET/CT	13.1	99.6	1.1	12.7	99.7	0.5
Stage IIIA							
	CE + CT	4.1	99.3	0.8	4.2	99.4	0.4
	CE + PET/CT	13.0	99.8	0.9	12.2	99.8	0.4
Stage IIIB							
	CE + CT	9.7	98.4	1.4	9.0	98.5	0.7
	CE + PET/CT	25.8	99.5	1.7	24.7	99.6	0.7
Stage IIIC							
	CE + CT	14.3	97.3	1.8	12.8	97.6	0.8
	CE + PET/CT	34.8	99.1	2.0	32.3	99.2	0.8

Key:
CE = clinical examination
CT = computed tomography of the chest, abdomen, and pelvis
PET = positron emission tomography
PPV = positive predictive value for detecting regional or distant recurrences
NPV = negative predictive value for detecting regional or distant recurrences

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Obesity and Peritoneal Surface Disease: Outcomes Following Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) K.I. Votanopoulos,* K. Swett, D.S. Swords, P. Shen, J.H. Stewart, E. Levine. *Wake Forest University, Winston Salem, NC.*

Background: It is estimated that 35% of the US population is obese. It is unknown how obesity influences the operative and survival outcomes of CRS/HIPEC procedures. Methods: A retrospective analysis of a prospective database of 1000 procedures was performed. Type of malignancy, ECOG, resection status, hospital and ICU stay, Clavien-Dindo morbidity, mortality and survival were reviewed. Results: 242 patients with BMI>30 (30-63.3) underwent 264 CRS/HIPEC procedures between 1991-2012. 94(38.8%) of those had a BMI>35. 136(51.7%) obese patients had appendiceal and 59(22.4%) colon cancer. Median follow up for obese patients was 52 months. Major (III /IV) and minor morbidity (I/II) was 36.6% and 28.8% for obese and 36.5% and 25.7% for non-obese patients. The 30 day mortality for obese and non- obese was 5.5% and 7.3% respectively. Median ICU and hospital stay was 1 and 9 days for both obese and non-obese. The 30 day readmission rate was similar between obese and non-obese patients 35.2% vs 30.8%. When patients were grouped by primary (colon or appendix), resection status, and grade of disease (for appendiceal) and stratified by BMI (not obese, 30-<35, ≥35) there was no difference in 30 day postoperative morbidity and mortality. When the interaction of obesity with the biology of the underlying primary was studied there was no obesity related survival differences. For obese and non-obese patients, median survival for low grade appendiceal cancer was 76 months and 107 months respectively (p=0.38) and for colon cancer was 18.1 months and 19.8 months. 5 and 10 year survival for the low grade appendiceal group was 60.5% and 33.1% for obese and 69.1% and 46.5% for non obese (p=0.38). Conclusions: Obesity does not influence postoperative morbidity and mortality of patients with peritoneal surface disease (PSD) regardless of primary. Obesity does not influence long term survival for appendiceal and colon cancer patients with PSD, and should not be considered a contraindication for the procedure.

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Identification of Age-Dependent Transition Zone in the Use of Internet/Electronic Devices is Important for Healthcare Communication in Cancer Patients A. Saied,* J. Espat, S.J. Sherry, D. Castricone, K.M. Perry, P. Somasundar. *Surgery, Roger Williams Medical Center, Providence, RI.*

Introduction: In this rapidly changing electronic era, we would like to define the age dependent variations in access and use of Internet/electronic devices in the exchange of healthcare related information (HRI) and coordination of clinical care (CCC) for cancer patients. Methods: Data was collected through independently completed surveys after obtaining IRB approval in a single institution cancer center during a 4-month period. Questions regarding internet access and use of electronic media to obtain health information and coordinate care were distributed. The sample was divided in two groups, one <65 y/o (group A) and a second group ≥65 y/o (group B), following the World Health Organization (WHO) age definition of geriatric patients. The data was compared between the two groups and statistical analysis was done using SPSS. Results: One hundred and twenty six surveys were analyzed with 70 patients in group A and 56 in group B. Access to the Internet and use of email was higher in the group A (77% and 71%) vs. group B (35.7% and 32.7%), (p<0.001). The younger group felt more comfortable using the Internet when compared to the older group (69.6% vs. 40% p=0.01). Both groups preferred paper based health information and phone calls to coordinate clinical care appointments over text messages or emails (60.6%, 75% for group A and 73%, 94.6% for group B). A transition zone between ages of 64 and 70 years was observed relative to access and use of internet and electronic devices to exchange HRI and CCC. Conclusion: The data supports that there is an age defined gap in the access and use of internet and electronic devices to exchange HRI and CCC. Characterization of this age dependent transition zone is important to target future strategies to improve delivery of HRI and CCC to the different age groups. This transition zone may be dynamic or remain constant depending on multiple factors which are difficult to identify and evaluate. In either case healthcare providers will need to rapidly adapt, using the appropriate tools to ensure quality in the exchange of HRI and CCC.

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General Surgery Resident Operative Experience in Surgical Oncology Over Two Decades S. Kwon,[1]* G.N. Mann,[1] P. Wu,[2] F. Drake,[1] K. Gow.[3] *1. General Surgery, University of Washington, Seattle, WA; 2. Veterans Affairs Puget Sound, Seattle, WA; 3. Seattle Children's Hospital, Seattle, WA.*

Introduction: Surgery resident education has seen significant changes over two decades. While surgical oncology is considered important part of educational objectives of a general surgical trainee, the operative experiences in surgical oncology cases have not previously been studied. Methods: The Accreditation Council for Graduate Medical Education case logs were retrospectively analyzed from academic years (AY) 1989-1990 to 2010-2011 for surgical oncology cases. Data were combined into five blocks: Period I (AY1989-90 to AY1993-94), Period II (AY1994-95 to AY1998-99), Period III (AY1999-00 to AY2002-03), Period IV (AY2003-04 to AY2006-07), and Period V (AY2007-08 to AY2010-11). Period IV and V were delineated by implementation of duty hour restrictions. Analysis of variance was used to compare means among the time periods with significance defined as $p < 0.05$. Results: The average number of surgical oncology cases increased from 176 in Period I to 217 cases in Period V. There were significant increases of surgical oncology cases from Period I

to II and Period II to III but there were no significant changes from Periods III through V. There was an increase in proportion of surgical oncology operations relative to total number of operations from 19.0% to 22.5% in this time period. When analyzing individual oncology procedures by RRC category, the largest proportion came from breast (35.8%) followed by colorectal (26.1%), endocrine (12.8%), skin/soft tissue (7.6%), thoracic (6.3%), hepatobiliary (3.3%), pancreas (2.8%), head and neck (2.3%), genitourinary (1.5%), esophagus (1.2%), and pediatric (0.2%). Increases were noted for some subcategories (colorectal, endocrine, skin and soft tissue, thoracic, hepatobiliary, pancreas) while decreases were noted in others (breast, head and neck, genitourinary) in the study period. Conclusions: General surgery residents perform an increasing number of surgical oncology operative cases and was not effected by the duty hour restrictions. In contrast to emergent abdominal and trauma operations, our findings demonstrate that general surgery trainees are performing more elective operations such as surgical oncology.

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Comparative Analysis of 2nd and 3rd Chemotherapy Lines on Short and Long-Term Survival of Elderly Medicare Metastatic Colon Cancer Patients N. Hanna,[1]* E. Onukwugha,[2] K.A. Bikov,[2] Z. Zheng,[2] B. Seal,[3] D. Mullins.[2] *1. University of Maryland School of Medicine, Department of Surgery, Division of General & Oncologic Surgery, Baltimore, MD; 2. University of Maryland School of Pharmacy, Department of Pharmaceutical Health Services Research, Baltimore, MD; 3. Bayer Healthcare pharmaceuticals. Inc, Wayne, NJ.*

BACKGROUND Metastatic colon cancer (mCC) patients often receive multiple lines of chemotherapy as treatment (TX) to improve survival or quality of life, yet the "real world" benefits and risks of multiple TX lines have not been fully examined. METHODS Elderly (65+) SEER-Medicare patients diagnosed with mCC in 2003-2007 were followed until death or 12/31/2009 to examine the survival benefits for different chemotherapy lines. The median time between diagnosis date and the starting date of 2nd line was 352 days. Therefore, we restricted comparative analysis of 2nd and 3rd chemotherapy TX lines to patients who survived at least 1 year after mCC diagnosis date. We used Cox regression framework and adjusted for patients' TX and censoring histories by using inverse probability weighting method. Separate analyses were conducted for short (2 years) and long-term (5 years) survival to examine different benefits of 2nd and 3rd chemotherapy lines. RESULTS Of 2,600 elderly Medicare mCC patients diagnosed between 2003-2007 and who survived at least 1 year, 2,530 were dead by the end of 2009. Significant factors associated with long-term survival (Table) were 1st line therapy(HR = 0.76; p < 0.01), 2nd line therapy (HR = 0.83; p < 0.01), and 3rd line therapy(HR = 0.85; p = 0.04), as compared to no therapy, age groups 95+ (HR = 3.07; p < 0.01), 85-94 (HR = 1.33; p < 0.01), and 75-84 (HR = 1.10; p = 0.04) as compared to 65+-74, Asian vs. White (HR = 0.71; p < 0.01), and zip code level household median income (HR = 0.98; p = 0.01). For short-term survival, the benefits of 2nd and 3rd line therapy were maintained until month 29. Patients with poor performance status were less likely to proceed to 2nd line therapy. No statistically significant variables predicting receipt of 3rd line chemotherapy were identified. CONCLUSIONS Among elderly Medicare mCC patients who survived at least 1 year after diagnosis, 1st line therapy improved both short and long-term survival. 2nd and 3rd line therapy reduced short-term mortality (2 years); however, they didn't add any additional long term survival benefit (5 years) as compared to 1st line therapy.

Survival Analysis With 1 Year Washout Period

		5-Year Survival Analysis N = 2600; Died: 2530			2-Year Survival Analysis N = 1290; Died: 1249		
		HR	95% CI	p-value	HR	95% CI	p-value
CCI (Reference: CCI=0)	CCI = 3	1.12	(0.91, 1.38)	0.27	1.14	(0.86, 1.52)	0.36
	CCI = 2	0.93	(0.80, 1.09)	0.38	1.08	(0.86, 1.35)	0.52
	CCI = 1	1.03	(0.93, 1.13)	0.59	0.93	(0.81, 1.08)	0.34
Proxies for Poor Performance Status:	Hospital Bed Use	1.58	(0.78, 3.21)	0.21	1.81	(0.68, 4.82)	0.23
	Oxygen Use	1.19	(0.93, 1.52)	0.16	0.93	(0.68, 1.29)	0.68
	Walking Aid Use	0.58	(0.31, 1.09)	0.09	0.87	(0.30, 2.52)	0.80
	Wheel Chair Use	0.80	(0.57, 1.13)	0.21	0.80	(0.46, 1.40)	0.43
Chemotherapy (Reference: No treatment)	3rd Line TX	0.85	(0.72, 0.99)	0.03	0.57	(0.45, 0.72)	<.0001
	2nd Line TX	0.83	(0.75, 0.93)	0.00	0.65	(0.56, 0.76)	<.0001
	1st Line TX	0.76	(0.68, 0.84)	<.0001	0.82	(0.70, 0.95)	0.01
Age Groups (Reference: 65-74)	95+	3.07	(1.89, 4.98)	<.0001	0.86	(0.47, 1.56)	0.61
	85-94	1.33	(1.15, 1.54)	0.00	1.22	(1.00, 1.48)	0.05
	75-84	1.10	(1.01, 1.19)	0.04	1.00	(0.88, 1.13)	0.99
Race/Ethnicity (Reference: White)	Others	0.86	(0.41, 1.83)	0.70	0.98	(0.34, 2.84)	0.97
	Asian	0.71	(0.56, 0.89)	0.00	0.84	(0.61, 1.16)	0.30
	Hispanic	0.98	(0.81, 1.20)	0.88	0.73	(0.55, 0.97)	0.03
	African American	1.10	(0.95, 1.27)	0.21	0.87	(0.71, 1.07)	0.19
SES:	State Buy-In Status	1.01	(1.00, 1.02)	0.14	1.02	(1.00, 1.04)	0.02
	Household Median Income	0.98	(0.96, 0.99)	0.01	1.00	(0.97, 1.03)	0.79

CCI: Charlson Co-morbidity Index
SES: Socioeconomic status

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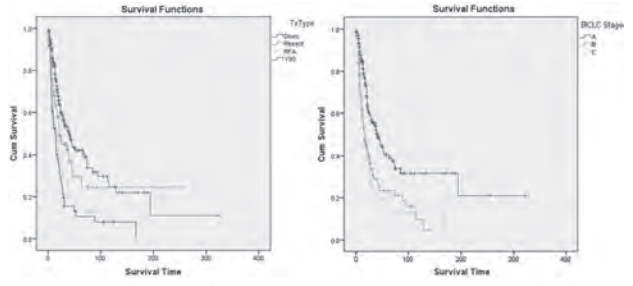
Evaluation of Initial Staging and Treatment in Prognosis of Hepatocellular Carcinoma Patients N. Burnett,* E. Dunki-Jacobs, G.G. Callender, R. Anderson, C.R. Scoggins, K.M. McMasters, R.C. Martin. *University of Louisville, Louisville, KY.*

Background Hepatocellular carcinoma (HCC) is one of the top five most common cancers in the world and one of the top three most common causes of mortality worldwide. The aim of this study was to evaluate overall survival (OS) of a South-Midwest patient population separated into four different treatments (Resection, Thermal ablation, Doxorubicin Drug Eluting Beads, and Yttrium-90 spheres). Methods A prospective hepatopancreaticobiliary (HPB) database was reviewed for all patients diagnosed with HCC between 1/2000 to 6/2012. Patients were categorized by BCLC classification and treatment modality. Kaplan-Meier (KM) analysis was performed to determine OS for each treatment as well as for each treatment when matched stage-for-stage. Results Among Doxo Bead patients, 143 (52%) were BCLC A, 88 (32%) were BCLC B, 27 (10%) were BCLC C. Among resection patients, 58 (81%) were BCLC A, 12 (17%) were BCLC B, and 2 (3%) were BCLC C. Among Ablation patients, 23 (70%) were BCLC A, 8 (25%) were BCLC B, and 2 (3%) were BCLC C. Among Yttrium-90 patients, 9 (14%) were BCLC A, 31 (48%) were BCLC B, 20 (31%) were BCLC C. KM analysis and survival curves showed a significant difference in survival between BCLC stages (log-rank p<0.0001) and between treatments (log-rank p<0.0001). The 1 and 5 year OS was 87% and 50% respectively for Doxo Bead therapy, 77% and 41% for resection, 64% and 26% for Ablation, and 53% and 12% for Yttrium-90. Doxo Bead therapy showed a significant difference in overall survival between stages (log-rank p<0.0001) while no other treatment reached significance. Conclusion Traditionally, resection and transplantation have produced the most favorable outcomes among eligible HCC patients based on initial BCLC stage. In our patient population, better outcomes are reported for Doxo Bead therapy as the initial treatment. Often, Doxo Beads are as an induction therapy of patients in order to better understand the biology of the HCC and assess

the functional reserve of the liver. Initial BCLC stage may not be as important to survival outcomes as induction therapy assessment after 3 months and continual reevaluation of stage following each treatment interval (i.e. every 3 months).



Kaplan Meier Survival Curves for Treatment modality and BCLC stage

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Quality of Life after Cytoreductive Surgery and Hyperthermic Intra-Peritoneal Chemotherapy–An Asian Perspective W. Tan,* G. Tan, C. Chia, K. Soo, M. Teo. *Department of Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore.*

Background Although Cyto-reductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has gained acceptance for the treatment of peritoneal carcinomatosis, the data on quality of life (QOL) after treatment remains scarce, particularly among the Asian population. This study aims to assess long term patient rated outcomes and QOL post CRS and HIPEC in an Asian cancer centre. Methods All patients who completed CRS+HIPEC between 6 to 18 months ago were enrolled in the study. QOL was measured via the administration of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires by 2 healthcare professionals. The scores were compared with a control group consisting of QOL scores obtained from 393 disease free cancer patients not on active treatment but on routine follow up. The one sample t-test was used to compare differences in QOL scores between the 2 groups of patients. Results 20 patients were analysed of which 16 (80%) were females. Median age was 50 years (36 – 69 years). CRS + HIPEC was performed for ovarian cancer in 11 patients (55%) and appendiceal carcinoma in 5 patients (25%). The other primary tumours include Colorectal carcinoma (2 patients), primary peritoneal carcinoma (1 patient) and endometrial carcinoma (1 patient). The median intra-operative Peritoneal Carcinomatosis Index (PCI) score was 11 (4 - 27) while the Completeness of Cytoreduction (CC) Score was 0, 1 and 2 in 15, 4 and 1 patients respectively. The median duration post CRS+HIPEC was 12 months (6 – 16 months). The QOL scores of patients post CRS+HIPEC compared to that of the control group are illustrated in Table 1. Global health status, functional and symptom scores were largely similar between our cohort of patients and the control group. Cognitive functioning scores and fatigue scores were significantly better in the group post CRS + HIPEC with a 95% Confidence Interval for difference of 2.8 to 15.6 (p=0.007) and -21.15 to -2.8 (p=0.013) respectively. Conclusion Despite the initial morbidity associated with CRS and HIPEC, long term QOL in survivors can be comparable to that of disease free cancer patients.

Table 1

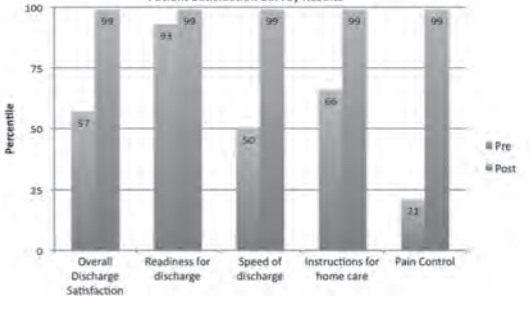
QOL Parameter	Mean Score of Study Population (95% Confidence Interval)	Control (n=393)	p value
Function Score			
Global Health	75.0 (66.6 - 83.4)	70.5	0.443
Physical Functioning	87.1 (77.9 - 96.2)	85.3	0.431
Role Functioning	90.2 (78.4 - 102.0)	86.7	0.396
Emotional Functioning	86.3 (77.0 - 95.6)	80.7	0.117
Cognitive functioning	89.2 (81.8 - 96.6)	80.8	0.007*
Social Functioning	91.2 (82.0 - 100.3)	86.0	0.406
Symptom Score			
Fatigue	13.7 (3.3 - 24.1)	25.3	0.013*
Nausea and vomiting	7.8 (-1.8 - 17.5)	4.3	0.338
Pain	13.7 (2.7 - 24.8)	18.1	0.660
Dyspnoea	11.8 (1.4 - 22.1)	15.1	0.317
Insomnia	15.8 (5.0 - 26.4)	24	0.060
Appetite Loss	11.8 (-0.3 - 23.8)	11.3	0.943
Constipation	13.7 (1.5 - 25.9)	11.5	0.974
Diarrhoea	13.7 (0.1 - 27.3)	5.7	0.191
Financial Difficulties	17.6 (2.7 - 32.6)	22.8	0.424

* denotes statistically significant results

P252

Addition of a Dedicated Inpatient Nurse Practitioner to a Busy Surgical Service Improves Discharge Efficiency and Patient Satisfaction R.S. Sweeting,* M.O. Meyers, B. Brower, E.A. Spain, I.R. Dickinson, A.A. Meyer, H.J. Kim. *Surgery, UNC Chapel Hill, Durham, NC.*

Introduction: The use of physician extenders is growing in response to increasing resident work hour restrictions and public policy on health care calling for more efficient delivery of health services. However, there are few studies which have assessed the actual benefits of physician extenders in a systematic way. We present data demonstrating the impact of the addition of a dedicated nurse practitioner (NP) to a busy surgical oncology service at an academic teaching hospital. Methods: Discharge data was reviewed from 7/2011 to 1/2012 in order to capture a 2 month period prior and 5 month period following the addition of the NP. Discharge hour, discharge cycle time (DCT), and Press Ganey survey data on patient satisfaction were assessed. DCT is the interval between physician entry of discharge order and the time the patient leaves. Results: A total of 431 discharges were evaluated. There was a statistically significant shift towards discharges earlier in the day, from 15:30 to 14:23 ($p < 0.001$) with a concomitant improvement in turnover time as seen in the decrease in DCT from 5:27 (CI 23:52,-12:57) to 3:45 (CI 12.18, -4.47). Patient satisfaction increased by all measures related to the discharge process including overall discharge satisfaction, readiness for discharge, speed of discharge, instructions for home care and pain control, with all post NP percentiles of 99% compared to pre-NP percentiles ranging from 21-93%. Conclusion: The addition of a dedicated nurse practitioner resulted in improved discharge efficiency, patient satisfaction and patient knowledge. The implications for improved health care delivery are significant.



P253

Failure of Surgical Oncology Education in General Surgery Residency C.J. Wai,[1]* Z. Maher,[2] T. Li,[1] K. Devarajan,[1] D. Crawford,[1] A.A. Thomay,[1] E.R. Sigurdson,[1] J.M. Farma.[1] *1. Fox Chase Cancer Center, Philadelphia, PA; 2. Temple University, Philadelphia, PA.*

Introduction: The National Comprehensive Cancer Network (NCCN) is an alliance of 21 cancer centers that establishes treatment guidelines for cancer. The American Board of Surgery requires general surgery residents to develop clinical knowledge and management skills in surgical oncology. The aim of our study was to evaluate surgical residents' exposure to surgical oncology and knowledge/use of the NCCN guidelines. Methods: An anonymous electronic survey was sent to the chairman and program directors of the 250 ACGME general surgery residencies for distribution to all residents in their program. Questions examined residents' demographics, training year, tumor board attendance, and knowledge/use of the NCCN guidelines. Results: There were 485 residents that responded and demographics are in Table 1. A total of 94% of residents attended tumor boards and attendance was greater with each increasing year of training (p=0.02). Tumor board attendance was infrequent in 40% while 38% attended weekly. Eighteen percent of respondents never heard of the NCCN, 21% did not know about their cancer guidelines, and 12% of those who have heard of the guidelines have never used them. Of the residents that never used the NCCN guidelines, 40% are PGY 1, 34% are PGY 2-3, and 26% >PGY 4. Greater knowledge of the guidelines (p=0.0003) and use of the guidelines (p<0.0001) existed with each increasing year of residency. Only 56% learned about the guidelines from faculty. There was no difference in use and knowledge by type of training program. Regional differences existed in attendance at tumor boards (p=0.004) with lower attendance in the Northeast and increased use of the guidelines in the Midwest (p=0.04). Conclusions: Of residents who responded, 21% have no knowledge of the NCCN guidelines and an additional 12% have never used them despite knowing they exist. Overall, 30% of residents have never used the NCCN guidelines. Our study identifies an important opportunity to improve surgical residency training in the U.S. and ultimately the care of cancer patients as many general surgeons will be managing and operating on cancer patients.

Table 1. Characteristics of respondents

Characteristics	n
Training Program Type	
Academic	329 (68%)
Community	125 (25%)
Military	18 (4%)
Hybrid	13 (3%)
Year of Training	
PGY 1	125 (26%)
PGY 2-3	171 (35%)
PGY 4 and above	189 (39%)
Region of Training	
West	42 (9%)
Midwest	109 (22%)
South	150 (31%)
Northeast	184 (38%)

P254

Return to Intended Oncologic Treatment (RIOT): A Novel Metric for Evaluating the Efficacy of Open and Minimally Invasive Surgical Oncology G. Zimmitti,* J. Vauthey, J. Shindoh, A.B. Cooper, C.D. Tzeng, S.A. Curley, T.A. Aloia. *Surgical Oncology, the University of Texas MD Anderson Cancer Center, Houston, TX.*

Introduction: For many patients (pts) with advanced malignancy, multimodality treatment strategies indicate the delivery of postoperative oncologic therapies. After surgical resection, however, complications and disability prevent some pts from receiving further treatment. Given that an inability to complete all intended therapies may negate some or all of the benefits of surgical therapy, strategies to improve return to intended oncologic therapy (RIOT), including prehabilitation and minimally invasive surgical (MIS) approaches, are being advocated. Material and Methods: To examine the incidence of and risk factors associated with an inability to RIOT in liver surgery pts a homogenous cohort of 223 pts who underwent open resection of metachronous colorectal liver metastases was identified. To specifically focus on outcomes after MIS approaches, a second group of 24 pts treated with MIS hepatectomy for malignancy was also assessed. Results: Of the 223 open surgery pts, 167 were offered postoperative therapy (156 accepted and 11 declined) yielding a RIOT rate of 75%. The remaining 56 (25%) pts were unable to receive further treatment due to delayed recovery from complications in 29 pts and poor performance status in 27 pts. Risk factors independently associated with the inability to RIOT were hypertension (OR 3.8, p=0.014), multiple preoperative chemotherapy regimens (OR 7.8, p=0.006), and postoperative complications (OR 3.3, p=0.015). Although the spectrum of liver operations was different between the two groups with less major hepatectomies in the MIS group, transfusion rates (0% vs. 16.6%, p= 0.030) and length of stay (3.7 days vs. 6 days open, p<0.001) were lower in the MIS group. In contrast to the open group, 100% of MIS pts who were intended to initiate postoperative therapy did so (p=0.038) at a median time interval of 15 days (range: 5-36 days). Conclusion: For both open and minimally invasive oncologic surgery, studies should report RIOT rate as an additional quality indicator. When oncologically equivalent, MIS approaches that may be associated with higher RIOT rates should be considered.

P255

Sequential Immune Monitoring of Melanoma and Renal Cell Carcinoma Patients Treated with High-dose Interleukin-2 (IL-2): Immune Patterns and Prognosis D.M. Foureau,* A. Amin, H. Norton, T. Sarantou, I.H. McKillop, R.L. White, J.S. Salo. *General Surgery Research, Carolinas Medical Center, Charlotte, NC.*

IL-2 therapy leads to cancer remission in 10-25% of patients with metastatic melanoma (MMEL) or renal cell carcinoma (MRCC). To date, no biomarkers have been validated to identify patients likely to respond. Aims. We hypothesized that changes in T-cell subset prevalence in patients undergoing IL-2 therapy correlates with treatment outcomes and sought to characterize their immune profiles. Methods. Thirty patients (15 MMEL, 15 MRCC) underwent retrospective immune monitoring through 3 courses (2 cycles each) of IL-2 therapy. For each cycle, peripheral blood mononuclear cells were sampled prior to receiving IL-2 (720,000 IU/kg), during (at least 3 doses) and after treatment (30±6h after last dose). Circulating T-cell subset prevalence was assessed by flow cytometry and correlated to patient's clinical response to IL-2. Results. IL-2 induced a transient drop of circulating CD4/CD8 T-cell ratios that returned to baseline at the conclusion of each cycle. A longer lasting IL-2 effect was observed on CD4 CD25hi Foxp3+ (Treg) and CD8 Foxp3+ T cells that expanded gradually during each cycle. Multifactorial measure of variance analysis showed a higher degree of variability in MMEL patient immune profiles during IL-2 therapy than MRCC patients. Among the immune variables tested, CD4, CD8 T-cells and CD4 Treg prevalence at baseline did not correlate with treatment outcome. MMEL patients that did not respond to IL-2 had more CD8 Foxp3+ T cells (0.27±0.12%) than patients with stable or responsive disease (0.1±0.02 and 0.14±0.1%). In addition, MMEL patients that responded to IL-2 therapy had, at baseline, at least twice as many CD25+ lymphocytes as the non-responding population. Neither CD8 Foxp3+ nor lymphocyte CD25 expression had prognostic value in MRCC patients. Conclusions. MMEL patients receiving IL-2 showed more heterogeneous immune profile than MRCC patients. A specific immune profile at baseline characterized MMEL patients that failed to respond to IL-2 therapy: elevated CD8 Foxp3+ T cell prevalence and overall low CD25 expression, which may be useful to predict IL-2 responsiveness in MMEL patients.

P256

A Cost Analysis of Somatostatin Use in the Prevention of Pancreatic Fistula after Pancreatectomy R. Anderson,* E. Dunki-Jacobs, G.G. Callender, N. Burnett, K.M. McMasters, C.R. Scoggins, R.C. Martin. *University of Louisville, Louisville, KY.*

Background: Many studies have shown that prophylactic somatostatin reduces the incidence of post-operative pancreatic fistula. However, few studies have analyzed the cost effectiveness of this treatment. The aim of this study is to analyze the cost effectiveness of somatostatin use with respect to pancreatectomy. Methods: A review was performed of a prospectively collected 2002 patient hepato-pancreatico-biliary database. Patients were included if they underwent pancreatectomy from 01/01/2007 to 05/31/2012. Patients received somatostatin prophylactically at the discretion of their surgeon. Data were analyzed using univariate analysis to determine if somatostatin ($206.75/dose) had any effect on imaging costs, lab costs, "other" costs, pharmacy costs, PT/OT costs, surgery costs, room and board costs, and total hospital costs. Results: We identified 179 patients who underwent pancreatectomy

(65 Whipple and 14 distal pancreatectomy patients received somatostatin and 74 Whipple and 26 distal pancreatectomy patients did not) at a single teaching institution. Median total hospital costs were $90,673.50 ($59,979-$743,667) for patients who developed a post-operative pancreatic fistula versus $86,563 ($39,190-$463,601) for those who did not (p=0.004). Median pharmacy costs for all patients receiving somatostatin was $11,827 ($1,334-$169,251) versus $7,502 ($1,749-$104,060) for all patients not receiving somatostatin (p=0.347). Median room and board costs for all patients receiving somatostatin was $15,040 ($3,955-$91,944) versus $15,276 ($4,155-$97,386) for all patients not receiving somatostatin (p=0.608). Median total hospital costs were $89,369 ($39,190-$743,667) for patients who were administered somatostatin versus $85,291 ($40,092-$463,601) for patients who did not (p=0.821). Conclusion: Pancreatic fistulas significantly increase hospital costs and somatostatin has been shown to decrease the rate of pancreatic fistula formation. Somatostatin has no significant effect on hospital costs. Therefore, somatostatin use has been shown to improve clinical outcomes post-pancreatic resection and does not significantly increase hospital costs.

Table: A comparison of median hospital costs in US dollars, by department, for all patients who underwent pancreatectomy who received versus did not receive somatostatin

Cost in Dollars	Somatostatin	No Somatostatin	p-value
Imaging	1,724 (0-60,683)	1,460 (0-46,666)	0.996
Lab	14,143 (4,556-219,059)	13,940 (2,837-94,774)	0.730
Other	4,703 (189-149,698)	4,090 (23-74,018)	0.654
Pharmacy	11,827 (1,334-169,251)	7,502 (1,749-104,060)	0.347
PT/OT	1,502 (0-8,554)	1,209.50 (0-6,648)	0.744
Surgery	34,223 (17,762-74,184)	39,576.50 (16,727-124,517)	0.001
Room and Board	15,040 (3,955-91,944)	15,276 (4,155-97,386)	0.608
Total	89,369 (39,190-743,667)	85,291 (40,092-463,601)	0.821
Total Minus Surgery	49,537 (10,620-692,568)	43,133 (9,820-416,051)	0.738
Room and Board Plus PT/OT	16,951 (3,955-93,877)	15,864.50 (4,155-102,473)	0.654

P257

The Extent of Radical Lymph Node Dissection Influences Survival of Patients with Melanoma S. Pasquali,[1]* N. Mozzillo,[3] A. Maurichi,[4] C.R. Rossi,[2] P. Quaglino,[5] L. Borgognoni,[6] N. Solari,[7] D. Piazzalunga,[8] L. Mascheroni,[9] G. Giudice,[10] S. Mocellin,[1] R. Patuzzo,[4] C. Caracò,[3] S. Ribero,[5] U. Marone,[2] M. Santinami.[4] *1. Dept. of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; 2. Veneto Institute of Oncology, Padova, Italy; 3. National Cancer Institute Pascale, Napoli, Italy; 4. National Cancer Institute, Milano, Italy; 5. University of Torino, Torino, Italy; 6. Ospedale S.M. Annunziata, Firenze, Italy; 7. National Cancer Research Institute, Genova, Italy; 8. Ospedali Riuniti, Bergamo, Italy; 9. Casa di Cura Pio X, Milano, Italy; 10. University of Bari, Bari, Italy.*

Introduction. The effect of the extent of radical lymph node dissection (RLND) on survival of melanoma patients is still unproven. This study sought to 1) investigate the effect of the extent of RLND on survival, 2) search for subgroups of patients who may benefit from a more extended RLND and 3) identify minimum number of lymph nodes (LNs) that should be excised. Methods. Retrospective data from patients treated at 9 centers were gathered in a multi-institutional database. Results. The study encompassed 2,536 patients. At multivariate analysis, the number of excised LNs (as continuous variable) was an independent predictor of melanoma-specific survival (HR 0.99, P=0.011). Patients with 21-30 (HR 0.702, P=0.011) and >30 (HR 0.675, P=0.017) excised LNs have significant lower risk of death than patients with < 11 excised LNs. In subgroup analyses, the number of excised LNs was a prognostic factor in patients having an intermediate thickness melanoma (T2, HR 0.97, P=0.011; T3, HR 0.97, P=0.002), but not in those with thin (P=0.689) or thick (P=0.804) tumors. The number of excised LNs influenced survival of patients who have had a groin RLND (HR 0.98, P=0.013), but not a neck RLND (P=0.573). A borderline non-significance difference was achieved for axillary RLND (P=0.066). The number of excised LNs influenced survival of patients with 2-3 positive LNs (HR 0.97, P=0.005), but not that of patients with a single positive LN (P=0.418) or > 3 positive LNs (P=0.717). The number of excised LNs predicted prognosis of patients with micrometastasis (HR 0.98, P=0.009), but not in case of macrometastasis (P=0.423). Patients with micrometastasis from intermediate thickness melanoma (N=1,090, 43%) experienced a greater survival when 12, 9 and 11 LNs were excised at axillary, inguinal and ilio-inguinal RLND, respectively. Conclusions The extent of RLND affected survival of patients with LNs metastasis, particularly in case of micrometastasis from an intermediate thickness melanoma. In these patients, 12, 9 and 11 LNs should be excised at axillary, inguinal and ilio-inguinal RLND, respectively. Further evidence is required to validate these findings and investigate neck dissection.

P258

Nerve Integrity Monitoring (NIM) in Parotid Surgery: Increase of Quality for Patient and Training of Surgical Residents? C. Van Berlo,* P. Nijhuis. *Surgery, VieCuri Medical Centre, Venlo, Netherlands.*

Introduction: Identification and preservation of the facial nerve is crucial in parotid surgery. In experienced hands, parotid surgery will result in less than 1% of facial nerve dysfunction. Small numbers of patients make it difficult to teach the technique to residents. We studied whether the systematic use of NIM would be helpful in teaching this procedure to our residents. Patients: From January 2007 till August 2012 in 44 patients a NIM guided surgical resection of the parotid gland was performed. In 11 cases NIM-guided smaller resections were performed rather than a superficial parotidectomy. Residents performed part of these procedures. Results: Per-operatively even the slightest traction or pressure resulted in a clear acoustic signal, leading to more cautious manipulation by surgeon and resident. None of the patients showed any post-operatively persistent damage of the facial nerve. All tumors were excised with adequate margins. Conclusions: In accordance with the literature, there was no difference in long-term facial nerve injuries compared to our series of parotidectomy without NIM-guidance, we published earlier in 2000 (Dutch Society of Surgery). Nevertheless, teaching this procedure to residents was facilitated using the acoustic feedback of NIM in case of too much traction or pressure on the branches of the facial nerve. NIM enabled us to teach even minimal invasive parotid surgery in a controlled and safe way. We feel that this monitoring is of great use in teaching parotid surgery.

P259

An Analysis of Disparities in Surgical Oncology Trials for Lung Cancer T. Ahmad,[1]* E. Song,[1] G. Russell,[1] M. Howard-McNatt,[1] R.A. Bell,[2] J.H. Stewart.[1] *1. Wake Forest School of Medicine, Department of Surgery, Winston-Salem, NC; 2. Wake Forest School of Medicine, Maya Angelou Center for Health Equity, Winston-Salem, NC.*

Background: Little work has evaluated factors attributing to disparities in participation in surgical oncology trials for lung cancer in the United States The work contained herein details participatory patterns in these trials . Methods: The NCI Cooperative Group Surgical Oncology (CGSOT) database was queried for patients with breast, prostate, colorectal, and lung cancer between 2000 and 2011 (n=15,958). Enrollment fraction (EF), which is defined as the number of enrollees per 1000 estimated cancer cases in each demographic group, was the primary outcome measure. Geographical Information Systems data were used to evaluate regional healthcare and socioeconomic characteristics for each patient. Independent t-tests were utilized to assess differences in patient characteristics. Results: We found that 1,892 participants in the NCI CGSOT database were diagnosed with lung cancer. These patients were less likely to participate in surgical oncology trials than those with breast, prostate and colorectal cancers (EF=0.70vs2.70, p<0.0001). As expected, the vast majority of participants in surgical oncology trials for lung cancer were white (92.1%,O.R.=1.44, p<0.001), and male (97.4%,O.R.=44.4, p<0.001). Interestingly, most of the patients in this cohort were older than 55 years of age (87.7%,O.R.=5.6, p<0.001). As with other tumors, white patients had higher rates of participation than minority patients (E.F.=0.94 vs.0.34, p=0.026). Unlike previous studies, participants older than 65 years of age were as likely as their younger cohorts to participate in surgical oncology trials for lung cancer (E.F.=0.879 vs.1.15, p=0.106). There was no difference in the participation by gender in this cohort of patients. Conclusion: Our findings suggest that patients with lung cancer are less likely to participate in surgical oncology trials than those with other primary tumors. We found race-based inequities in participation in surgical oncology trials for lung cancer. Future work will focus on interventions that not only will improve the recruitment of patients to these trials, but ones that will also reduce racial disparities in participation in surgical oncology trials.

P260

The Quality of Our Quality Reporting: Metrics of Cancer Care Following Pancreatoduodenectomy J.B. Liu, R.E. Schwarz, G.C. Balch, A.C. Yopp, J.C. Mansour.* *Surgical Oncology, University of Texas Southwestern, Dallas, TX.*

Introduction: Metrics of quality cancer care for patients following pancreatoduodenectomy have been incompletely defined. One of the first steps towards defining quality cancer care is identifying those variables associated with outcome. We hypothesized that predictive variables for these patients would be inconsistently reported in the surgical literature. Methods: We performed an English-language NLM PubMed search to identify unique, large, original studies describing variables predictive of patient outcome following pancreatoduodenectomy for cancer. We considered 37 variables putatively described as outcome predictors in five domains: patient characteristics, operative factors, postoperative events, tumor characteristics, and multidisciplinary/treatment-planning. Studies were reviewed to identify which potentially predictive variables were reported. Differences in reporting rates between domains were assessed by univariate analysis using Student's t-test and ANOVA. Results: Our search initially identified 529 studies reporting series of patients undergoing pancreatoduodenectomy. Sixty studies met inclusion criteria. The most common reasons to exclude studies included: small patient numbers, no outcome predictors identified, not cancer-focused. The rate of reporting any variable from a specific domain varied widely (Table 1). All studies reported at least one patient characteristic and one tumor-related variable. Rates of reporting at least one technical (82%), postoperative (83%), treatment-planning (90%) variable were consistent. The mean frequency of studies reporting individual multidisciplinary/treatment-planning variables was significantly less than the frequency of reporting variables from other domains. Conclusions: The reporting of potential factors contributing to outcomes of cancer patients undergoing pancreatoduodenectomy is inconsistent. Multidisciplinary/treatment-planning variables are less frequently presented than patient, tumor, technical, and postoperative factors. Inclusion of a complete set of defined and potentially relevant predictive factors may allow for the development of more comprehensive and robust metrics of quality cancer care.

Reporting of cancer care variables by domain

Domain	Variables (n)	Mean (%)	Range (%)	p-value*
Patient Characteristics	6	49	13 - 100	0.0154
Technical Factors	5	40	30 - 60	0.0062
Postoperative Factors	5	46	17 - 72	0.0061
Tumor Characteristics	8	48	5 - 100	0.0045
Multidisciplinary/treatment planning	13	18	0 - 51	ref

* as compared to multidisciplinary/treatment planning variables

P261

Socio-Demographic Factors and Their Impact on the Number of Resections for Patients with Recurrent Glioblastoma Y. Sia,* K. Field, M. Rosenthal, K. Drummond. *The Royal Melbourne Hospital, Melbourne, VIC, Australia.*

Introduction: Glioblastoma (GBM) is the most aggressive malignant brain tumour. Having a second or subsequent operation at recurrence may be a positive prognostic factor for survival. Recent studies suggest that socio-demographic variables may influence survival; raising the question whether surgical care differs based on these variables. Methods: We examined the relationship between selected socio-demographic variables and the number of repeat operations undergone by patients with recurrent GBM. Data from all patients diagnosed with GBM between 2001 and 2011 was obtained from a clinical database at two institutions. The clinical and socio-demographic factors for patients who received one operation were compared to those who had two or more (≥2) operations, using chi-square analyses to determine statistical differences between groups. Socio-economic status was measured using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) scores. Results: Of 553 patients, 449 (81%) had one operation and 104 (19%) had ≥2 operations. Patients who had ≥2 operations were significantly younger (median 55 years versus 64 years, $p<0.001$), less likely to have multifocal ($p=0.043$) or bilateral ($p=0.037$) disease and more likely to have initial macroscopic resection ($p=0.006$), than those who had only one operation. Socioeconomic status did not significantly differ between the groups ($p=0.31$). Similarly, there was no significant difference between the number of operations in patients from regional versus city residence and public versus private hospital. Conclusion: There were no significant differences between the socio-demographic status of patients who had multiple resections for recurrent GBM and those who had only one operation. This is reassuring in that it suggests that similar surgical management options are available for patients regardless of their socio-demographic background.

P262

Geographic Variability for Pancreatectomy in Patients with Stage I and II Pancreatic Adenocarcinoma: Low Resection Rates Predict Worse Outcome B. McDowell,* J.R. Howe, E.A. Chrischilles, J.J. Mezhir. *University of Iowa, Iowa City, IA.*

Introduction: Low usage of pancreatectomy for Stage I/II pancreatic cancer in the US has been reported, yet it is not clear to what extent this reflects under-utilization of resection versus appropriate selection of operative candidates. To address this, we examined the geographic variation in pancreatectomy. Methods: We queried the US Surveillance, Epidemiology, and End Results (SEER) research data for Stage I and II adenocarcinoma of the pancreatic head diagnosed from 2004-2009. Factors included in the multivariate analyses (MVA) were age, gender, race, stage, and geographic region. The primary endpoints were rate of pancreatectomy and median overall survival. Results: 10,520 patients with Stage I (n=2,068) and Stage II (n=8,452) pancreatic head cancer were analyzed. Pancreatectomy was performed in 528 patients (25.5%) with Stage I disease and in 4,295 patients (50.8%) with Stage II disease (overall resection rate=45.9%). Rates of resection significantly varied across the 18 SEER regions after controlling for age, gender, race, and stage ($p<0.0001$). For the analysis, the SEER regions were divided into groups of high, medium, and low rates of resection (56.3%, 46.6%, and 41.1%, respectively). Median survival of patients in the high resection regions was 12 months (95% CI=11-12 months), which was significantly longer than in low and medium resection regions (both=10 months, 95% CI=9-10 months, $p<0.0001$). MVA confirmed that regions with high resection rates are associated with improved survival while controlling for age, gender, and race (Table). Conclusions: Pancreatectomy rates vary highly across geographic regions, and areas with higher rates of resection are associated with better outcome. These data may reflect poor adherence to treatment guidelines, which possibly reflects a lack of confidence in the effectiveness of pancreatectomy or expertise in performing the procedure. Studies that control for patient selection factors are underway to further elucidate these important findings.

Results of multivariate analysis for overall survival.

Variable	Hazard Ratio	p-value
Age (vs. >=80 years)		
40-49 years	0.397	<0.0001
50-59 years	0.402	<0.0001
60-69 years	0.446	<0.0001
70-79 years	0.599	<0.0001
Gender		
Male vs. Female	1.026	0.272
Race (vs. other*)		
White	0.988	0.809
Black	1.224	0.001
Resection Region (vs. Medium rate region)		
Low rate region	0.974	0.315
High rate region	0.853	<0.0001

*American Indian, Alaska Native, Asian/Pacific Islander

P263

Demographic Risk Factors Impacting Quality Radiation Therapy Completion after Breast Conserving Surgery B.D. Powers,* M.P. Daly, J.A. Montes, T. Lambert, A. Willis. *Surgery, Temple University School of Medicine, Philadelphia, PA.*

Background Quality radiation therapy completion (QRTC) is critical to quality breast conserving treatment (BCT). Our aim was to identify patient groups at greatest risk of not achieving QRTC in BCT in an urban setting. Methods Hospital Tumor Registry Data years 2004 – 2009, was collected for female BCT patients Stages I and II. Radiation therapy completion (RTC) was defined as 35 days or more of breast radiation. QRTC was defined as RTC of 35-49 days. Logistic regression was performed with SPSS. Results 346 patients were analyzed. The racial distribution was: Black n=230 (66.5%), White n=63 (18.2%), Hispanic n=53 (15.3%). Age distribution was: < 50 years n=74 (21.4%), 50 – 64 years n=152 (43.9%), > 64 years n=120 (34.7%). Insurance distribution was: Medicare n=131 (37.9%), Private n=94 (27.2%), Medicaid n=121 (35.0%). Hispanic patients (60.4%) were more likely to have Medicaid than Blacks (33%) or Whites (20.6%), $p<0.001$. The majority (52%) of patients

lived within 3 miles of the hospital radiation oncology treatment facility. More Blacks (66.5%) lived within <3.0 miles of the facility than Whites (7.9%) or Hispanics (41.5%), p<0.001. There was no difference in mean days of RTC by ethnicity (Black 46.8, White 46.4, and Hispanic 48.1 days; p=0.75) or total RTC % (Black 88.2%, White 97.9%, Hispanic 93.3%; p=0.09). However, a substantial difference was seen in QRTC % by ethnicity (Black 51.8%, White 79.2%, Hispanic 57.8%; p=0.03). Multivariate logistic regression analysis of failure to achieve QRTC found associations with black race (OR=2.67), Medicare (OR= 3.46), Medicaid (OR=2.19), and age <50 years (OR=4.13). Conclusion This study demonstrates high overall percentage RTC; however, it identifies there are actually substantial disparities in successful QRTC. Those at greatest risk of unsuccessful QRTC were younger, Medicare or Medicaid insured, and black race. Distance category was not a significant factor in this urban population. Further studies should investigate the specific barriers that may contribute to disparities in QRCT among these at risk groups.

	OR	95% CI	p-value
Race			0.082
White	1.00		
Black	2.67	1.13-6.33	0.026
Hispanic	2.03	0.80-5.38	0.152
Age			0.008
>64	1.00		
50-64 yrs	1.33	0.55-3.19	0.527
<50 yrs	4.13	1.45-11.76	0.008
Insurance			0.026
Private	1.00		
Medicare	3.46	1.33-9.00	0.011
Medicaid	2.19	1.02-4.67	0.043
Stage			0.815
I	1.00		
II	0.94	0.54-1.63	
Distance			0.439
<3.0 miles	1.00		
≥3.0 miles	0.79	0.44-1.42	

Logistic regression of risk factors for quality radiation therapy completion after breast conserving surgery

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Economic Evaluations in Surgical Oncology - A Systematic Review S.S. Brar,[1]* I. Datta,[2] F.A. Quereshy.[1] *1. University of Toronto, Toronto, ON, Canada; 2. University of Calgary, Calgary, AB, Canada.*

INTRODUCTION: Innovations within oncology have led to improvements in quantity and quality of life, but can be associated with significant costs. Projections suggest that the costs of cancer care may increase drastically. Economic evaluations are needed to assess both clinical outcomes and costs of new surgical oncology interventions. The methodological quality of the existing literature in economic evaluations of surgical oncology is unknown. METHODS: A systematic review of all economic evaluations involving surgical interventions in oncology between 2005 and 2011 was completed using the Tufts Medical Centre Cost-Effectiveness Analysis Registry and the NHS Economic Evaluation Database. Quality assessment of studies was completed using a 35-point checklist developed for economic evaluations. RESULTS: The literature search yielded 47 economic evaluations that were included for analysis. For study design, 23 were cost-utility analyses 21 were cost-effectiveness analyses and 2 were cost-benefit analyses, and was justified in 74% of studies. In measuring outcomes, 35% of studies have design and results from a single-study described and 46% described the method of synthesis of multiple studies. Of the cost-utility studies, 83% stated the methods of valuing health states. Quality assessment scores ranged from 44-94%, and these scores have remained relatively constant over the 5 year study period. For costing, methods for the estimation of quantities and unit costs were described in 85% of studies, though only 17% reported quantities and unit costs separately and only 20% included productivity changes. For analysis, the time horizon was stated in 78% of studies and only 50% stated a discount rate for costs and/or benefits. 78% of studies reported a sensitivity analysis along with their economic evaluations. Learning curve effects and volume-outcome relationships were not included in these studies. CONCLUSIONS: Economic evaluations in surgical oncology are of variable methodological quality. Improvements in methodology and adherence to established standards are of paramount importance. Further work is necessary to adapt economic evaluations to the assessment of surgical interventions.

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Surveillance after Curative-intent Treatment for Breast Carcinoma: The Effect of Initial Stage T. Mishra,[1] J.A. Margenthaler,[2] E.S. Allam,[1] L. Chen,[2] K.S. Virgo,[3] F.E. Johnson.[1]* *1. Saint Louis University Medical Center, St. Louis, MO; 2. Washington University Medical Center, St. Louis, MO; 3. American Cancer Society, Atlanta, GA.*

Introduction: The American Society of Clinical Oncology (ASCO) has published surveillance guidelines based on randomized trials. We recently reported data showing that there is remarkable variation from guidelines in the intensity of surveillance among clinical experts. We sought to determine how much of the variation is due to the initial TNM stage. Methods: We created a survey instrument that featured 4 idealized vignettes, each depicting a generally healthy middle aged woman with a breast cancer of a particular TNM stage. We identified as clinical experts the 3,245 ASCO members who indicated that breast cancer was a major focus of their clinical practice. The survey was delivered by internet. The experts were offered 12 testing modalities which the relevant literature indicates are commonly used for surveillance. They were asked how they would conduct surveillance for the patients described in the vignettes for 5 years after treatment. A two-way ANOVA model was employed to determine which surveillance modalities were recommended statistically significantly differently according to TNM stage. Significance was set at p<0.05. All tests were two-sided. Results: The response rate for the survey was 31% (1012/3245). 915 (90%) of the responses were evaluable and were analyzed further. The most frequently recommended modality for screening was office visit for all 4 vignettes (Table). Other commonly recommended modalities included CBC, LFTs and mammogram. The frequency of recommended use was statistically significantly different across TNM stage for all modalities. For 10 of the 12 modalities, the recommended frequency of utilization decreased significantly with increasing post-treatment year. Conclusions: ASCO experts often recommend surveillance modalities not endorsed by ASCO guidelines, suggesting overuse. Although ASCO surveillance guidelines are not stratified by TNM stage, clinical experts stratify their surveillance strategies based on TNM stage. The actual variation in surveillance intensity attributable to TNM stage, even though statistically significant, was clinically rather small and cannot explain the known remarkable variation we have previously reported.

Number of recommended office visits (mean ± SD) per year stratified by TNM stage.

Stage	Year 1	Year 2	Year 3	Year 4	Year 5
0	2.8 ± 1.2	2.5 ± 1.2	2.1 ± 1.3	2.0 ± 1.4	1.9 ± 1.5
IIA	3.3 ± 1.3	3.0 ± 1.1	2.4 ± 1.1	2.2 ± 1.1	2.1 ± 1.3
IIB	3.3 ± 1.2	3.0 ± 1.1	2.5 ± 1.2	2.3 ± 1.3	2.2 ± 1.3
IIIA	4.1 ± 2.2	3.3 ± 1.2	2.7 ± 1.3	2.5 ± 1.3	2.4 ± 1.3

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Importance of Operative and Pathology Data Accuracy to Maximize Quality of Reporting in Stage II Resectable Pancreatic Cancer B.C. Buder,[1]* S.S. Reddy,[2] K.S. Martin,[1] M. Wayne,[1] F. Attiyeh,[3] S.T. Brower.[1] *1. Beth Israel Hospital NYC, New York, NY; 2. Fox Chase Cancer Center, Philadelphia, PA; 3. St. Luke's Roosevelt, New York, NY.*

The ability to collect, interpret and analyze operative reports and pathological data are essential to adequately stage and deliver proper goal directed adjuvant therapies in stage II pancreatic cancer. The purpose of our study is to identify accuracy of reporting what intra-operative factors affect pathological staging, by means of analyzing operative dictations and final pathological assessment. Over the course of 5 years we performed 221 pancreaticoduodenectomies, and we evaluated a recent group of 42 patients who had complete operative and pathologic information. We graded superior mesenteric vein (SMV) margins as either being clear (52%) or borderline resectable (48%). Overall, 36% of patients were described in the operative report as having underwent a lymph node dissection. Knowing that CBD, pancreas and SMA margins are important, we observed frozen sections margins of these structures were performed 31%, 43%, 10% respectively as mentioned in the operative

report. Upon specimen removal, these margins were marked by the surgeon 10%, 10%, 7% respectively. Analysis of pathologic reports revealed the average nodal harvest was 15, with the median number of postive nodes 2. 14% of patients were N0. We wanted to assess if a clinical description of clear or borderline resectable correlated with lymphovascular (LVI) or perineural (PNI) invasion. It was shown that LVI and PNI was 44% and 88% in clear, while in the borderline it was 55% and 94% (P=NS). The pathologist inked specimens 82% of the time. CBD and pancreas margins were evaluated 100%, however only 63% of SMA margins were described. Pathologically, our R0 resection rate was 74% overall. We have demonstrated that the surgeon's descriptions of important factors related to pancreas cancer is a significant target for quality improvement. In addition, communication of the surgeon with the pathologist occurred in the minority of cases. Similar quality initiatives in examining all relevant margins related to an R0 resection exist for the pathologist. This has led us to instituting a communication pathway between surgeon and pathologist for the reporting of pancreatic resection.

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Breast Cancer in Patients with Schizophrenia: Compliance with Adjuvant Radiation Therapy L.M. Davies,[1]* K. Abdullah,[1] R. Janardhan,[1] M.C. Hwang,[1] M. Farasatpour,[1] J.A. Margenthaler,[2] K.S. Virgo,[3] F.E. Johnson.[1] *1. Saint Louis University Medical Center, Saint Louis, MO; 2. Washington University Medical Center, Saint Louis, MO; 3. American Cancer Society, Atlanta, GA.*

Introduction: Schizophrenia is common. It impairs the clinical course of patients with unrelated physical disorders. We evaluated how patients with schizophrenia who are later diagnosed with breast cancer fare when adjuvant radiation therapy (ART) is clinically indicated. Methods: We searched Patient Treatment File (PTF), the national inpatient database of the Department of Veterans Affairs (DVA), to identify patients with schizophrenia who subsequently developed breast cancer and were treated in DVA Medical Centers (DVAMCs) between 1999 and 2005. PTF data was supplemented with chart-based clinical information from the DVAMCs where the patients had been treated. Results: We identified 126 patients through the initial search. Fifty-six patients were considered potentially evaluable. Forty-two patients had preexisting schizophrenia, later developed breast cancer, and were candidates for ART according to well-established guidelines; these patients comprised our data set. There were 31 women (74%) and 11 men (26%). Twenty-seven of the 42 study subjects had records specifying TNM stage; 18 (67%) of the 27 had TNM stages III-IV. We found data regarding compliance with indicated medical therapies in 31 subjects; 24 (77%) had previously been non-compliant with care. Of the 42 patients who were considered candidates for ART based on TNM stage, we found data about the decision to offer ART in 37; only 23 (62%) were offered ART and 6 of those 23 (26%) refused it. Conclusions: Patients with schizophrenia who are subsequently diagnosed with breast cancer often do not fare well if offered clinically indicated ART. They often do not understand the nature of their illnesses well and do not comply with recommended standard therapies. A history of prior non-compliance with recommended standard therapies appears to be a strong predictor of non-compliance with ART. Treatment strategies that rely on ART are likely to be met with non-compliance. Our results should be of interest to surgical oncologists because breast-conserving multimodality treatment is frequently not appropriate; radical surgery is often indicated.

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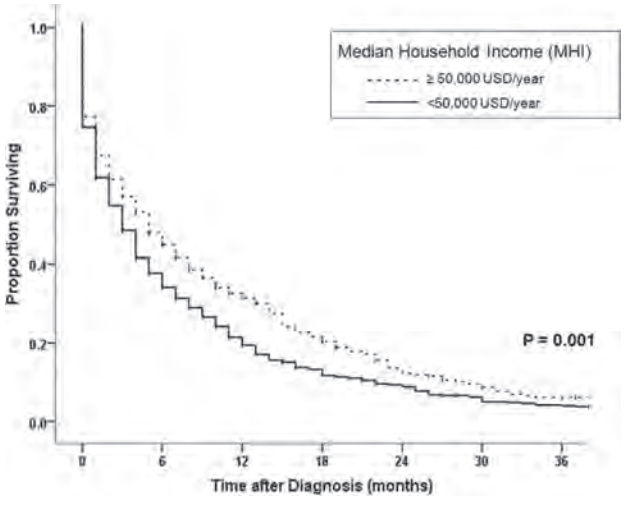
Income Inequality Affects Treatment and Survival of Patients with Intrahepatic Cholangiocarcinoma - A Texas Cancer Registry Analysis P. Kneuertz,* L.S. Kao, T.C. Ko, C.J. Wray. *Department of Surgery, University of Texas Medical School at Houston, Houston, TX.*

INTRODUCTION: Intrahepatic cholangiocarcinoma (IHC) is often diagnosed at advanced stage and few patients qualify for resection. Effects of barriers to healthcare access on outcomes given the short therapeutic window are unknown. We hypothesized that low income and rural residence account for delays in treatment and decreased survival. METHODS: The Texas Cancer Registry (TCR) was queried for patients diagnosed with IHC between 2000-2008. Median household income (MHI) based on county of residence and urban/rural status derived from census tract data were analyzed amongst standard clinicopathologic factors. MHI was dichotomized around $50,000/year. Univariate and multivariate regression analyses were performed for the endpoints (1) time to initiation of treatment (TTT), and (2) overall survival (OS). RESULTS: Among 1,089 patients, mean age was 68.4 years and 54.8% were male. Of 452 patients with completed staging, 56.2% had localized disease. MHI ranged from $24,497 to $81,113/year and 20.2% patients resided in rural areas. Primary treatment included surgery for 98 (9.0%), radiation for 52 (4.8%) and chemotherapy for 216 (19.8%) patients. Median TTT was 29 (range 0-235) days. Patients from lower income counties were less likely to initiate treatment (MHI<$50.000/year, 31% vs. ≥$50,000/year, 38.1%; p=0.02). MHI<$50,000/year was associated with longer TTT (hazard ratio (HR) = 0.80 [95% confidence interval (CI): 0.65-0.99]; p=0.04). Median OS for the entire cohort was 4 months and associated with treatment (surgery, 17 months vs. radiation, 7 months vs. chemotherapy, 8 months vs. none, 2 months; p=0.001). Adjusted for stage and type of treatment, low MHI was associated with decreased OS (MHI<$50,000/year: HR = 1.34 [95%CI: 1.09-1.65]; p=0.005). Rural residence was neither associated with TTT nor OS. CONCLUSION: Low income and not urbanization was associated with delayed initiation of treatment and decreased survival after diagnosis of IHC independent of stage and treatment modality. Further research is needed to determine how regional poverty relates to care access to overcome survival disparities of patients with IHC.



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Radioactive Iodine Overuse for Low Risk Micropapillary Thyroid Carcinoma A.W. Chae, A.D. Yang, S.R. Martinez.* *Surgery, University of California-Davis, Sacramento, CA.*

Background: We have previously shown that radioactive iodine (RAI) is overused in the adjuvant treatment of micropapillary thyroid carcinoma (MPTC). We aimed to report on clinical and pathologic factors associated with use of RAI among the lowest risk members of this population. Methods: The Surveillance, Epidemiology, and End Results database was queried for patients who underwent surgery for MPTC (tumor size ≤ 1 cm) from 1988 to 2009. We excluded patients without a biopsy-proven diagnosis, those diagnosed at autopsy, patients with documented extrathyroidal extension and lymph node metastasis. The final population included only those who had no nodal staging (NX) or were node-negative (N0). Multivariate logistic regression models predicted use of RAI based upon patient, tumor, and treatment-related factors. Results: Among 21,954 patients eligible for study inclusion 21,663 (98.7%) had complete information on the use of RAI. Of these, RAI was used in 22.7%. On multivariate analysis, Asian race/ethnicity (OR 1.39, CI 1.23-1.58; p<0.001) and increasing tumor size (OR 1.23, CI 1.21-1.24; p<0.001) predicted use of RAI. RAI use was less likely with black (OR 0.72, CI 0.62-0.85; p<0.001) or unknown race/ethnicity (OR 0.43, CI 0.28-0.67; p<0.001), advancing age (OR 0.99, CI 0.99-1.00; p<0.001), and those undergoing thyroid lobectomy (OR 0.14, CI 0.12-0.15; p<0.001), nodulectomy (OR 0.13, CI 0.08-0.23; p<0.001), or subtotal thyroidectomy (OR 0.48, CI 0.43-0.55; p<0.001). Conclusions: A significant number of even the lowest risk MPTC patients receive RAI. Until evidence supports a benefit of RAI in this population, its use should be discouraged.

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Is There Benefit in Reducing Time from Diagnosis to Treatment for Patients with Newly Diagnosed Breast Cancer? S. Misra,* A. Poirier, J. Booker, D. Ottersen, M. King, S. Ray. *Surgical oncology, Cancer Treatment Centers of America, Zion, IL.*

Introduction: Hospital patient satisfaction surveys suggest that a key driver of newly diagnosed breast cancer patients' decision to begin treatment is speed to treatment. The hospital initiated a lean six sigma project to reduce time from first patient contact to the patient receipt of a treatment plan in order to determine the effect on treatment rates. Methods: Initial data was gathered for the total population of newly diagnosed breast patients that consulted the hospital including: treatment starts, time from initial contact to treatment plan, patient satisfaction, and treatment rate. Based on analysis of this data, a new process was implemented that would allow patients to receive their individualized treatment plan within 24 hours of diagnostic workup. The new process included a team-based treatment plan consultation with the patient's medical oncologist, radiation oncologist and surgeon within 24 hours of completion of diagnostic testing. Results: The treatment rate for the five months pre-implementation (January 2011 thru May 2011) was 76.6%. The treatment rate post-implementation (January through May 2012) is 94.5%. Conclusions: The results of the implemented process suggest a higher treatment rate post-implementation. Patients benefited through equal or improved time measurements when comparing the time between the first appointment, obtaining a treatment plan and finally, getting treated. Patients opted to begin treatment sooner under this pathway. Minimal adjustments structurally within the facility were necessary. Patients support the new process and value the collective approach by the physicians in receiving their personalized treatment recommendation.

	5 months pre-implementation	5 months post- implementation
Time from 1st contact to appointment	7 - 10 days	3 - 5 days
Time from 1st appt. to treat after diagnostics completed	8.9 days	7.5 days
Treatment rate	76.6%	94.5%
Customer satisfaction	83%1	85%1

The hospital was unable to collect patient satisfaction data specifically for this specific patient population, but, the satisfaction rate for all breast cancer patients improved from 83% to 85% for this time period.

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Outpatient Mastectomy: Current Practice and Utilization Trends in California L. Uyeno,* L. Streja, S.L. Chen, C. Vito, J. Yim, L. Kruper. *City of Hope, Duarte, CA.*

Background: Increasing outpatient mastectomy (OM) rates were first described in the late 1990's. Pressure to decrease hospital length of stay (LOS) and perform mastectomies in the ambulatory setting has been reported. However, current practice patterns and true rates of OM are unknown. Methods: The Healthcare Cost and Utilization Project (HCUP) captures inpatient hospital and ambulatory surgery center recorded procedures. We evaluated HCUP data for California from 2005-2009 to identify all women undergoing mastectomy. Influence of patient (age, race, income, insurance) and hospital (urban, ownership, size, LOS) characteristics by year and visit type (inpatient vs. outpatient) were determined by bivariate analysis using Jonckheere-Terpstra test for trend. A multivariate logistic regression model was used to examine predictors of OM. Results: During the five year period, 38,131 inpatient mastectomies (IM) and 13,963 OM were performed. The rates of both IM and OM have increased. However, the proportion of OM has increased (26% to 27.3%) and IM decreased (74% to 72.7%, $p<0.046$). Compared to younger patients ≤45, patients age 46-64 (OR 1.24 95%CI 1.17-1.32) and age≥65 (OR 1.35 95%CI 1.23-1.48) were more likely to have OM. Patients who were Asian (OR 1.42 95%CI 1.33-1.52) or Hispanic (OR 1.17 95%CI 1.1-1.25) had a higher likelihood of OM than white patients. Patients with Medicare (OR 1.22 95%CI 1.1-1.35) and private insurance (OR 1.5 95%CI 1.39-1.62) were more likely than Medicaid patients to undergo OM. Patients in urban areas were 1.5 times more likely to have OM than rural areas (OR 1.52 95%CI 1.38-1.67). Year of procedure and income were also significant predictors of OM. Conclusions: Mastectomy rates in California have been increasing with one-fourth of mastectomies performed as an outpatient. The proportion of OM has increased slightly though not uniformly across all populations. Determinants of OM were year, age, race, income, insurance, and hospital location. These findings suggest significant variations in practice and utilization. To better guide future policies, the influence of this variation on patient outcomes and cost will need to be further examined.

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Patient Surveillance after Breast Cancer Treatment: Variation Among Specialties R. Parmeshwar,[1] E.S. Allam,[1] L. Chen,[2] K.S. Virgo,[3] J.A. Margenthaler,[2] F.E. Johnson.[1]* *1. Saint Louis University Medical Center, St. Louis, MO; 2. Washington University Medical Center, St. Louis, MO; 3. American Cancer Society, Atlanta, GA.*

Introduction: Treatment strategies for potentially curable breast cancer are standardized. Data from high quality clinical trials of post-treatment surveillance strategies exist. We compared post-treatment surveillance methods employed by radiation oncologists (RO), medical oncologists (MO) and surgeons (SO) following potentially curative treatment for breast carcinoma. Methods: We designed a survey instrument with 4 vignettes describing generally healthy women with breast cancer of differing prognoses and emailed it to the 3245 American Society of Clinical Oncology (ASCO) members who indicated that breast cancer was a major focus of their practice. Respondents were asked to indicate how often they would use 12 specific surveillance modalities for such patients during years 1-5. Median, range, mean and standard deviation of frequency of use for each modality and vignette were determined. Results: Of the 3245 ASCO members surveyed, 1012 (31%) responded. Of these, 846 were evaluable. Respondents included 70% MO, 10% SO, and 5% RO; 15% did not specify. Significant variation in surveillance intensity among the 3 groups of experts was observed. RO recommended 3.1 ± 1.4 (mean ± SD) office visits in post treatment year 1; MO recommended 3.5 ± 1.6; SO recommended 3.0 ± 1.7 ($p<0.05$, ANOVA). The range of recommended office visits in year 1 was 0-12 for all 3 groups. For most other surveillance modalities, comparable variations were noted ($p<0.05$, ANOVA). Conclusions: Our survey results document marked variation in surveillance intensity according to specialty. Improved medical education is needed to inform clinicians and trainees about optimal post-treatment surveillance intensity.

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Do Factors That Significantly Predict 1st Line Treatment Also Predict 2nd Line Treatment for Elderly Metastatic Colon Cancer Patients? Z. Zheng,[1] E. Onukwugha,[1] N. Hanna,[2]* E. Reese,[1] B. Seal,[3] D. Mullins.[1] *1. University of Maryland, School of Pharmacy, Department of Pharmaceutical Health Services Research, Baltimore, MD; 2. University of Maryland, School of Medicine, Department of Surgery, Division of General & Oncologic Surgery, Baltimore, MD; 3. Bayer Healthcare Pharmaceuticals, Inc., Wayne, NJ.*

BACKGROUND Metastatic colon cancer (mCC) patients might receive multiple lines of chemotherapy to improve survival or quality of life. However, factors associated with receipt of 1st and 2nd line treatment (TX) haven't been fully investigated. METHODS Elderly (65+) SEER-Medicare patients diagnosed with mCC in 2003-2007 were followed until death or 12/31/2009 to examine factors for receipt of 1st and 2nd line TX. A Cox regression framework and inverse probability weighting (IPW) method were used to adjust for patients' informative (death) and non-informative (dropout or end-of-study) censoring histories. Additionally, we controlled for patients' 1st line TX in the IPW to determine factors for receipt of 2nd line TX. RESULTS Of 7,951 mCC patients, 3,266 patients received at least 1 line TX, and 1,440 went on to 2nd line TX. For 1st line TX, significant clinical factors (Table) were CCI = 2 (HR = 0.86; p = 0.02), oxygen use (HR = 0.74; p = 0.04), walking aid use (HR = 0.58; p = 0.02), and wheel chair use (HR = 0.50; $p < 0.01$); significant demographic characteristics were age groups 95+ (HR = 0.11; $p < 0.01$), 85-94 (HR = 0.24; $p < 0.01$), 75-84 (HR = 0.70; $p < 0.01$), as compared to 65+-74, female (HR = 1.12; $p < 0.01$), married (HR = 1.43; $p < 0.01$), and African American (AA) (HR = 0.80; $p < 0.01$); significant factors for socio-economics status were state buy-in status (SBI) (HR = 0.97; $p < 0.01$), and zip code level household median income (HR = 1.03; $p < 0.01$). For 2nd line TX, significant factors were hospital bed use (HR = 2.82; p = 0.05), oxygen use (HR = 0.68; p = 0.02), age group 85-94 (HR = 0.718; p = 0.02) as compared to 65+-74, and days delayed for 1st line TX (HR = 0.998; $p < 0.01$). CONCLUSIONS Various factors were associated with receipt of 1st line TX. Conditional on the receipt of 1st line TX, many factors became insignificant for receipt of 2nd line TX, such as age, female, marriage status, AA, SBI, and zip code level household income. Hospital bed use reduced the probability of receipt of 1st line TX, but increased the probability of receipt of 2nd line TX.

Factors Associated with Receipt of 1st and 2nd Line TX

		Receipt of 1st Line TX N = 7951; 1st Line TX: 3266			Receipt of 2nd Line TX N = 3266; 2nd Line TX: 1440		
		HR	95% CI	p-value	HR	95% CI	p-value
CCI (Reference: CCI=0)	CCI = 3	0.87	(0.74, 1.03)	0.10	0.98	(0.76, 1.25)	0.85
	CCI = 2	0.86	(0.76, 0.97)	0.02	0.96	(0.80, 1.16)	0.66
	CCI = 1	1.04	(0.97, 1.11)	0.32	0.97	(0.87, 1.08)	0.56
Proxies for Poor Performance Status:	Hospital Bed Use	0.61	(0.29, 1.27)	0.18	0.98	(0.76, 1.25)	0.85
	Oxygen Use	0.74	(0.60, 0.91)	0.004	0.96	(0.80, 1.16)	0.66
	Walking Aid Use	0.58	(0.36, 0.93)	0.02	0.97	(0.87, 1.08)	0.56
	Wheel Chair Use	0.50	(0.35, 0.73)	0.0003	0.98	(0.76, 1.25)	0.85
Age Groups (Reference: 65-74)	95+	0.11	(0.04, 0.28)	<.0001	1.41	(0.25, 7.93)	0.70
	85-94	0.24	(0.21, 0.28)	<.0001	0.72	(0.55, 0.94)	0.02
	75-84	0.70	(0.66, 0.75)	<.0001	1.08	(0.98, 1.18)	0.12
Race/Ethnicity (Reference:White)	Others	0.68	(0.41, 1.13)	0.13	1.26	(0.59, 2.69)	0.56
	Asian	0.98	(0.84, 1.14)	0.76	1.10	(0.88, 1.39)	0.41
	Hispanic	0.91	(0.79, 1.04)	0.15	0.94	(0.76, 1.17)	0.57
	African American	0.80	(0.72, 0.89)	<.0001	1.02	(0.86, 1.20)	0.86
SES:	State Buy-In Status	0.97	(0.96, 0.98)	<.0001	0.995	(0.98, 1.01)	0.55
	Household Median Income	1.03	(1.02, 1.04)	<.0001	1.007	(0.99, 1.03)	0.44
Female		1.12	(1.06, 1.19)	<.0001	1.06	(0.97, 1.16)	0.17
Married		1.43	(1.34, 1.53)	<.0001	1.04	(0.94, 1.15)	0.42
Urban		1.02	(0.91, 1.14)	0.77	0.99	(0.84, 1.17)	0.90

CCI: Charlson comorbidity index
SES: socioeconomic status

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Teleconferencing for Breast Cancer Multidisciplinary Conference P.F. McAuliffe,[1]* L. Hadzikadic Gusic,[1] K.P. McGuire,[1] A. Soran,[1] E.J. Diego,[1] S.L. Puhalla,[2] B.C. Lembersky,[2] D.V. Puleio,[3] M.L. Spangler,[4] W.A. Berg,[4] S. Beriwal,[5] R. Bhargava,[6] M.L. Gimbel,[7] S.L. Goldstein,[8] G.S. Engel,[9] M. Bonaventura,[1] G.M. Ahrendt,[1] R.R. Johnson.[1] *1. Surgical Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 2. Medical Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 3. UPMC Northwest, Pittsburgh, PA; 4. Radiology, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 5. Radiation Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 6. Pathology, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 7. Plastic and Reconstructive Surgery, Magee-Womens Hospital of UPMC, Pittsburgh, PA; 8. UPMC St. Margaret, Pittsburgh, PA; 9. UPMC Hamot, Erie, PA.*

INTRODUCTION: Multidisciplinary conferences increase communication between specialties to improve decision-making. As management of pts with breast cancer within health care systems extends to regional centers (RCs), it is a logistical challenge to bring experts together. We hypothesize that teleconferencing improves multidisciplinary case discussions. METHODS: Videoconferencing units linked to a bridging service were used for monthly Breast Cancer Multidisciplinary Teleconference (BCMT). Case presentations included pathology and radiology images and live discussions between all sites. Participants were e-mailed an anonymous survey covering practitioner demographics, AV quality and assessment of management. Travel time and miles from RCs to the flagship hospital (FH) were estimated using online maps. Results are mean ± standard deviation. Nominal data was compared using Mann-Whitney U Test. RESULTS: For the first 4 BCMTs, 4-6 sites participated; for the last 3, 7 did. In 7 BCMTs, 24 pt cases were presented. Each month, 38±7 practitioners attended: 29±14% and 71±14% from RCs and FH respectively, saving 973±465 miles and 17±8 travel hrs. 119 surveys evaluating BCMT were collected. Survey response rate was 42±16%, including 50±20% of FH and 32±19% of RC attendees (p=0.3). 32±11% and 68±11% were staff and physicians respectively. Of physicians who took the survey, 18±8% were trainees. Compared to their local cancer conference, 30%, 61% and 9% of respondents stated that BCMT led to a change in pt management more often, the same or less often, respectively; this was not different between FH and RCs (p=0.7), even if trainees were excluded (p=0.9). AV quality was scored outstanding or excellent by 71% of participants at the FH, but only 28% of participants at the RCs (p=0.002). Assessment of AV quality improved over time. Nevertheless, overall conference quality was rated outstanding or excellent by 75% of participants at the FH and by 64% at the RCs (p=0.7). CONCLUSIONS: The use of teleconferencing for BCMT has not previously been evaluated via survey in the US. Here we show it to be clinically useful, economical and time-effective. Further research is needed to determine improved breast cancer outcomes.

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A Contemporary Large Single Institution Evaluation of Retroperi-toneal Sarcoma Treatment: Have We Managed to Move Past the Scalpel Yet? P. Bremjit,* R.L. Jones, D.R. Byrd, G. Kane, X. Chai, E. Rodler, E. Loggers, S. Pollack, S. Gagnet, O. Kolokythas, J. White, B. Hoch, V.G. Pillarisetty, G.N. Mann. *University of Washington, Seat-tle, WA.*

PURPOSE. Retroperitoneal sarcomas represent roughly 10-15% of soft tissue sarcomas, a group which itself accounts for less than 1% of all solid tumors. These are challenging tumors to treat due to numerous factors. Surgical resection remains only treatment providing a means of cure. This retrospective study examined outcomes for patients following surgery and radiation or chemotherapy. METHODS. A study of all patients with retroperitoneal sarcomas referred to a university institution between Jan 2000 and April 2011 was performed. Demographics, tumor characteristics, treatment modalities, tumor response rate, and survival data were obtained from patient chart. Univariate Cox regression models described survival (OS) and recurrence-free survival (RFS) by tumor grade, resection type, and histology. RESULTS. The study identified 103 patients. Median follow-up was 40.3 months (2-257.3). Tumor grade was: low (n=26), intermediate (28), high (29) and not available (20). Histological subtype: leiomyosarcoma (n=17), liposarcoma (58), and other (17). Forty-one patients underwent complete microscopic resection (R0) and 36 underwent R1 resections. Median OS was 111 months and median RFS was 37 months. Patients with high grade tumors had significantly worse OS (p>0.0483) and worse RFS (p>0.0180). Maximal tumor dimension was a significant predictor for local recurrence (p>0.0393). Microscopic margin status and histological subtype were not found to be significant for OS or RFS. Of 29 tumors receiving neoadjuvant chemotherapy, 9 (31%) progressed, 14 (48.3%) were stable, 2 (6.9%) improved and 4 (13.8%) had unknown response. Of 31 tumors receiving neoadjuvant radiation, 2 (6.5%) progressed, 12 (38.7%) were stable, 17 (54.8%) had unknown response, and no patients improved. CONCLUSION. These data confirm that surgical resection should remain the mainstay of management for retroperitoneal sarcomas, with median OS of 111 months and RFS of 37 months. Neither neoadjuvant chemotherapy nor radiation was shown to significantly improve outcomes for patients, suggesting that these therapies have no role in the management of RPS in the neoadjuvant setting.

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Intra-Abdominal Metastatic Soft Tissue Sarcoma: Who May Benefit from Debulking Surgery? G. Lahat,* I. Nachmany, F. Gerstenhaber, D. Dayan, S. Abu-abied, O. Merimsky, R. Nakache, J.M. Klausner. *sur-gical oncology, Sourasky Medical Center, Tel Aviv, Israel.*

Background: In contrast to surgery for STS pulmonary metastases, an aggressive surgical approach towards intra-abdominal metastatic sarcoma (IMS) is controversial. This study analyzes prognostic factors associated with surgically treated IMS patients improved survival. METHODS: A retrospective STS database was reviewed; patients who had surgery for intra-abdominal metastatic STS between 1995 and 2012 were identified and are included in the study cohort. Analysis was performed using Kaplan-Meier estimates of survival, log-rank test, and multivariate Cox model. RESULTS: 53 patients had 71 operations for IMS; 33 patients (62%) had one operation, 15 patients (28%) had two, and five patients (10%) underwent three consecutive resections. Median age was 62 years (range, 28-82). Most patients (n=41; 77%) were treated for recurrent IMS; 56% (n=29) of primary tumors were retroperitoneal, high grade liposarcoma was the most frequent histological subtype (n=27; 51%). Complete macroscopic resection was documented in 59 cases (59%); 11 patients (21%) were additionally treated with hyperthermic intra-peritoneal chemotherapy. There was no intra- or perioperative mortality; morbidity rate was 28%. After a median follow-up length of 38 months (range, 2-297), intra-abdominal disease progression occurred in 32 patients (60%), pulmonary metastasis in 8 (15%), and both in 16 patients (30%). Overall five- year survival rate was 38% with a median survival of 32 months (range, 2-132). In multivariable analysis DFI > 12 months (HR: 2.77, CI 95% 1.05- 6.49) and completeness of resection; R0 vs. R1 and R2 (HR: 2.3, CI 95% 1.23-5.82) emerged as independent predictors of survival. Primary tumor location and histology, recurrent operations, number and/ or size of metastases, and the use of chemotherapy had no effect on survival. CONCLUSIONS: Aggressive surgical treatment of intra-abdom-

inal metastatic STS can be associated with prolonged survival. Tumor resectability and DFI are important factors for proper patient selection for curative surgery. Repeated metastasectomies may improve survival in select cases despite recurrent disease.

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Patients with Recurrent Retroperitoneal Sarcomas Benefit from Aggressive Surgical Resections A. Guzzetta,* C.M. Hooker, K. Ibrahim, E.E. Pappou, P. Dave, C. Wolfgang, T. Pawlik, E.A. Montgomery, N. Ahuja. *Johns Hopkins University, Baltmore, MD.*

Retroperitoneal sarcomas (RPS) continue to pose a treatment quandary because of their resistance to treatment and their tendency to recur multiple times. Current literature suggests that the first operation must be curative and subsequent resections for recurrence are of minimal benefit. This single-institution study instead suggests that with careful operative selection, patients may benefit from an aggressive surgical approach. Methods: A retrospective chart review was performed for all patients who received treatment for their RPS at our institution between 1984 and 2010. Kaplan-Meier survival curves and Cox-regression models were used to correlate patient and tumor characteristics with overall survival. Results: 227 patients met study criteria. Of these, 75.8% of patients presented with primary disease. 93.4% of patients underwent surgery following initial presentation and 63% had at least one recurrence. 35.2% of patients recurred once at a median time of 16.6 months, 15% recurred twice at 11 months, 7.9% recurred 3 times at 12.2 months and 5.3% recurred 4 or more times. Median overall survival was 43.4 months for patients with primary disease, 35.6 months for patients with a single recurrence, 65.5 months for two recurrences, 70.5 months for three recurrences, and 182.7 months for four recurrences. A Kaplan-Meier estimate of overall survival comparing total number recurrences suggests no difference in postoperative survival by number of recurrences with the exception of patients with 4 or more recurrences.(Fig 1). Multivariate analysis demonstrated that number of recurrences did not significantly correlate with overall survival ($p>0.05$). Age at surgery, metastasis upon initial presentation, positive resection margins and high tumor grade correlated with poor overall survival ($p<0.05$, all). Conclusion: All patients with resected RPS should be carefully followed after surgery regardless of their number of recurrences. The number of recurrences should not be considered as an absolute contraindication to surgery and carefully selected patients with surgically resectable and multiply recurrent RPS may enjoy a survival advantage from an aggressive surgical approach.

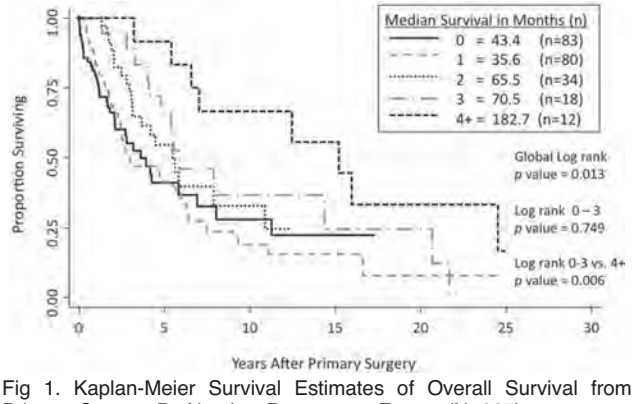

Fig 1. Kaplan-Meier Survival Estimates of Overall Survival from Primary Surgery By Number Recurrence Events (N=227)

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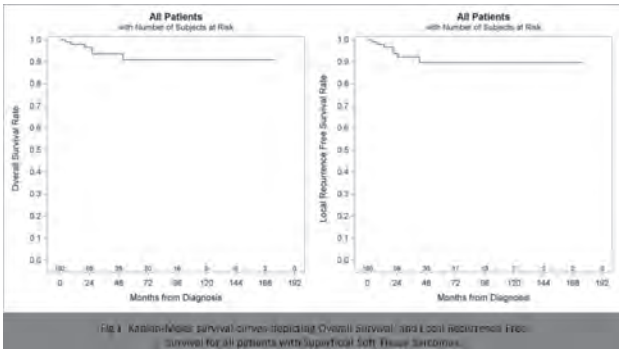
Superficial Soft Tissue Sarcomas – Homogenous Good Outcome in a Heterogeneous Group of Tumors S.S. Sanghera,[1]* V. Francescutti,[1] A. Miller,[1] R.A. Burke,[2] J.J. Skitzki,[1] J.M. Kane.[1] *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. Naval Medical Center, Portsmouth, VA.*

Introduction: The primary staging variables for soft tissue sarcomas (STS) are size, grade, and depth, but with limited emphasis on the latter. Superficial STS should be more amenable to negative margin wide excision. We hypothesized that local recurrence (LR) should be low, even without radiation (RT), and wondered how much "depth" contributed to overall survival (OS) Methods: A retrospective review (2002-2012) of all primary superficial STS patients undergoing definitive therapy. Patient demographics, tumor features, treatment, and outcome were analyzed. Results: There were 103 patients identified. Median age 54.5 years, 53% female. Primary tumor site was 39% trunk, 38% lower extremity, 14% upper extremity, 9% other. Common histologies were 36% leiomyosarcoma, 16% malignant fibrous histiocytoma. Median tumor size was 2.8 cm (range 0.2-14 cm). Sixty-six percent of tumors were intermediate/high grade. Preoperative RT was administered in 6%. Chemotherapy was given in only 7% (all angiosarcoma). An R0 resection was accomplished in 95%, 75% having > 2 cm margins. Skin graft was used in 22% and flap closure was required in 14%. Fifteen percent of patients received adjuvant RT. At a median followup of 48.6 months (range 34.2-176 months), there were only 9 patients with a LR (8.7%). Tumor size or grade was not associated with LR. Two patients (1.9%) developed lymph node metastases. Six patients (5.8%) developed distant metastases. There were no variables (including tumor size or grade) associated with OS on univariate analysis. Conclusions: LR was very low for superficial STS, even with larger or high grade tumors and with nominal use of RT. Negative margin surgical resection alone may be adequate therapy for most patients. Superficial location seems to supersede size and grade in terms of imparting an overall good prognosis for this heterogeneous group of tumors.



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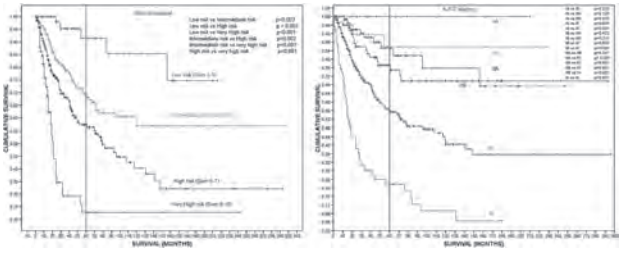
A Proposal for a New Staging System for Extremity Soft Tissue Sarcomas R.A. Salcedo-Hernandez,* L.S. Lino-silva, D. Cantú de León, H. Martínez-Said, A. Padilla-Rosciano, . Herrera-Gómez, A. Meneses-García, M. Cuellar-Hubbe. *Surgical Oncology, Instututo Nacional de Cancerología de México, Mexico, mexico, Mexico.*

Introduction. A universally acceptable staging system for soft tissue sarcomas (STS) is not available. The TS is underestimated because in most series the mean tumor size (TS) is 5-10 cm. We evaluated prognostic factors in 596 patients with extremity STS comparing the AJCC staging system against a new staging system (NS) that includes histologic grade (HG), TS, deep and resection margins. METHODS: Retrospective data of 596 patients with extremity STS collected from 1985 to 2010 were evaluated. The influence of clinical and pathological factors on recurrence, metastasis, and disease-specific survival (SV) was analyzed. We create the NS based in 4 parameters: A) HG: HG 1=1, HG 2=2, HG 3=3; B) Profundity: deep =1, superficial =0; C) TS: <5 cm =0; 5.1 to 10 cm =1; 10.1 to 15 =2; 15:1 to 20 = 3 and > 20 cm = 4; D) Surgical margins, R0 =0, R1 =1 and R2 =2. Adding A+B+C+D we created 4 risk stages: I) Low risk: score 1-3. II) Intermediate risk: score 4-5. III) High risk: score 6-7. IV) Very high risk: score 8-10. We compare the NS versus AJCC. RESULTS: The mean tumor size is 11.8 cm and >50% are >10 cm. Large TS and high HG were independent adverse prognostic factors for metastasis. Large TS, high grade, and R1 surgical margins were independent adverse prognostic factors for SV. There was a progressive decline in SV with increasing TS. AJCC staging did not correlate well with prognosis; the 5-yr-SV was 100% for Stage IA; 86% for both IB and IIA; 77% for IIB; 57% for III and 22% for IV. The SV difference between AJCC categories not was statistically significant in all cases: IA vs IB p=0.233, IA vs IIA p=0.123, IA vs IIB p=0.075, IB vs IIA p=0.472,

IB vs IIB p=0.211, IIB vs III p=0.001 and III vs IV p<0.001. Our novel score system showed differences between categories for 5-year SV, for stages I, II, III and IV were 92%, 69%, 57%, and 24%, respectively, with differences between each stage statistically significant (I vs II, p =0 .003, II vs III p=0.002, III vs IV p<0.001). CONCLUSION: Surgical margins, HG and TS are important determinants for metastases and SV. Our NS for extremity STS with emphasis on HG and TS is proposed. High correlation with SV and prognosis is found with this new system.



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Amputation for Extremity Sarcoma: Indications and Outcomes in the Modern Era D. Erstad,[1]* Y. Feng,[2] J. Ready,[3] J. Abraham,[4] M.L. Ferrone,[3] M.M. Bertagnolli,[5] E.H. Baldini,[6] C. Raut.[5] *1. Harvard Medical School, Boston, MA; 2. Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; 3. Department of Orthopedic Surgery, Brigham and Women's Hospital and Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute Hospital, Boston, MA; 4. Department of Orthopedic Surgery, Thomas Jefferson University, Philadelphia, PA; 5. Division of Surgical Oncology, Brigham and Women's Hospital and Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA; 6. Department of Radiation Oncology, Brigham and Women's Hospital and Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA.*

INTRODUCTION: Amputation, once the primary therapy for localized extremity sarcoma, is now rarely performed. We reviewed our experience to determine why patients (pts) with sarcoma still undergo immediate or delayed amputations, to identify differences based on timing of amputation, and to evaluate outcomes. METHODS: Records of pts with primary non-metastatic extremity sarcomas undergoing amputation at our institution from 2001-2011 were reviewed. Univariate analysis was performed to distinguish cohorts. Overall survival (OS), time to local recurrence (TLR) and metastasis-free survival (MFS) were calculated. RESULTS: We categorized 54 pts into 3 cohorts: primary amputation (A1, n=18, 33%), secondary amputation after prior limb-sparing surgery (A2, n=22, 41%) and hand and foot sarcomas (HF, n=14, 26%)(Table). Median age at amputation was 56 years (range 19-88); 59% were male. Common indications for amputation (>40% each) were loss of function, bone involvement and multiple compartment involvement in A1 pts; proximal location, multiple compartment involvement, multifocal or fungating tumor and loss of function in A2 pts; and joint involvement, prior unplanned surgery and no salvage options in HF pts; 89% had multiple reasons. Amputation was performed for non-oncologic reasons in 23% of A2 pts. Compared to A2 pts, A1 pts had more fungating tumors (p=0.03) but less joint involvement (p=0.03) and wider margins (p=0.002) at amputation. Compared to the A1/A2 cohorts, tumors in HF pts were smaller (p=0.0004), lower grade (p=0.03) and stage (p=0.0002), more superficial (p=0.01), involved a single compartment (p=0.001), were non-fungating (p=0.002), and had preserved limb function (p=0.0046). There was no significant difference in OS or MFS between cohorts (Table). Measured from date of 1st surgery, TLR was longer in A1 v. A2 pts (p=0.01) despite higher rates of radiotherapy in A2 pts, and in HF v. A1/A2 pts (p=0.02). CONCLUSIONS: Indications for amputation and tumor characteristics in pts with extremity sarcoma vary between the A1, A2, and HF cohorts. Though limb-sparing surgery remains standard of care, amputations chosen judiciously are associated with excellent disease control and survival.

		Primary Amputation n = 18 (% or range)	Amputation After Prior Limb-Sparing Surgery n = 22 (% or range)	Hand and Foot n = 14 (% or range)
Histology	Angiosarcoma	3 (17)	0	1 (7)
	Epithelioid Sarcoma	1 (6)	0	2 (14)
	Ewing Sarcoma	2 (11)	0	0
	Giant Cell Tumor	1 (6)	1 (5)	1 (7)
	Liposarcoma	1 (6)	1 (5)	2 (14)
	Myxofibrosarcoma	2 (11)	4 (18)	0
	Osteosarcoma	2 (11)	3 (14)	1 (7)
	Other	6 (34)	13 (59)	7 (49)
Median Tumor Size at Amputation, in cm		12.0 (2.9-30.5)	12.0 (1.9-40.0)	3.5 (1.3-10.1)
Grade	1	1 (6)	1 (5)	1 (7)
	2	0	1 (5)	2 (14)
	3	13 (72)	17 (77)	6 (43)
	Unknown	4 (22)	3 (14)	5 (36)
Indication for Amputation	Bone involvement	9 (50)	6 (27)	3 (21)
	Multifocal	4 (22)	9 (41)	3 (21)
	Prior Unplanned Surgery	1 (6)	3 (14)	6 (43)
	Fungating Tumor	6 (33)	12 (55)	0 (0)
	Pathologic Fracture	5 (28)	2 (9)	2 (14)
	Joint Involvement	2 (11)	8 (36)	7 (50)
	Neurovascular Compromise	5 (28)	8 (36)	1 (7)
	Proximal Location	7 (39)	18 (82)	0 (0)
	Loss of Function by Tumor	14 (78)	10 (45)	2 (14)
	No Salvage Possible for Positive Margins	1 (6)	4 (18)	9 (64)
	Multiple compartments involved	12 (67)	14 (64)	3 (21)
	Prosthetic failure	0 (0)	5 (23)	0 (0)
Overall Survival, in years	Median (90% CI); 5-year (90% CI)	Not reached (7.1-na); 89% (0.76-1)	8.7 (2.9-NA); 68% (0.52-0.85)	Not reached (8.0-na); 100% (1-1, only 1 event)
Metastasis-Free Survival, in years	Median (90% CI); 5-year (90% CI)	Not reached (3.1-na); 60% (0.4-0.8)	4.1 (2.4-NA); 50% (0.32-0.67)	Not reached (1.4-na); 64% (0.4-0.67)
Time to Local Recurrence, in years	Median (90% CI)	Not reached (1.7-na)	1.2 (1.0-1.8)	Not reached (6.5-na)

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Cutaneous Angiosarcoma: A Single Institution Review M.C. Perez,* T.A. Padhya, J.L. Messina, R.J. Gonzalez, M.M. Bui, G. Letson, C. Cruse, R.S. Lavey, M.R. Forster, V.K. Sondak, J.S. Zager. *Moffitt Cancer Center, Tampa, FL.*

Introduction: Cutaneous angiosarcoma (CAS) is a rare and aggressive vascular malignancy associated with poor long-term survival. Historically, AS is associated with a 5-year overall survival (OS) rate between 24-31%. Multimodality therapy is often used for local control and to treat metastatic disease. Methods: This retrospective review studied all patients (pts) treated at a tertiary referral center for CAS from 1999-2011, regarding demographics, tumor characteristics, treatment and outcomes, to identify predictors of survival and recurrence. Results: 88 pts were identified; median age was 70 and 57% were female. Median tumor size was 3 cm. 4 groups were identified; 1) XRT induced with a median of 9 years between XRT and presentation n=30 (34%), 26 of these occurred in the breast of females with a prior breast cancer 2) spontaneous CAS on head and neck (H/N) n=38; or 3) trunk/extremities n=13; and 4) lymphedema-associated (Stewart-Treves) n=7.Median follow-up was 22 months. 5-year (yr) OS and recurrence free survival (RFS) were 35.2% and 32.3%, respectively. Median survival was 22.1 months. Of the 67/88 pts disease-free after primary treatment, 33 (50%) experienced recurrence at a median of 7 months. Pts with Stewart Treves and CAS of the trunk/extremity had the highest 5-yr OS (Table) whereas those with H/N CAS had the worst 5-yr survival. 3 major treatment groups were identified; 36 (41%) pts received surgery alone, 7 (8%) received XRT alone, and 41 (47%) received surgery and XRT. Pts treated with surgery alone had the highest 5-yr OS (46.9%) and RFS (39.9%) although not significantly different from other groups on multivariate (MV) analysis. On MV analysis, only tumor size < 5 cm was found to correlate with improved OS (p= 0.014). Conclusion: In this large series, CAS pts were found to have a better prognosis than that which is historically reported, especially in CAS associated with Stewart Treves or outside of H/N. Tumor size was a significant prognostic factor for OS. While surgery alone as a pri-

mary treatment showed higher OS and RFS compared to XRT or surgery/XRT combined, this was not statistically significant.

Characteristic	No. of patients (%)	Median Overall Survival, months	Median Disease Free Survival, months	3-yr OS, %	5-yr OS, %	3-yr DFS, %	5-yr DFS, %
Age							
<70	41 (47%)	55.0	28.4	65.8	43.9	47.5	39.6
>=70	47 (53%)	34.0	21.0	45.3	27.7	34.5	25.9
Tumor Size							
<5	48 (62%)	55.0	28.0	64.5	48.4	42.6	42.6
>=5	30 (38%)	26.3	7.0	34.6	11.5	36.5	24.3
Margin Status							
+	18 (24%)	20.6	28.0	34.7	34.7	28.6	28.6
-	58 (76%)	52.8	25.4	64.3	37.9	43.8	33.4
Tumor Presentation							
Spontaneous Head and Neck	38 (43%)	35.5	25.4	49.3	21.5	33.7	0
Spontaneous Trunk/Extremities	13 (15%)	NE*	NE*	64.8	64.8	60.0	60.0
Stewart-Treves Syndrome	7 (8%)	38.4	6.4	66.7	NE*	0	0
XRT-Induced	30 (34%)	55.0	54.5	59.3	49.4	58.0	46.4
Local Treatment Modality							
Surgery + XRT	41 (47%)	37.3	16.9	58.4	30.9	27.9	27.9
Surgery Only	36 (41%)	59.5	41.4	60.2	46.9	59.8	39.9
XRT Only	7 (8%)	23.6	NE*	33.3	16.7	--	--

*Unable to be estimated due to small percentage of events (i.e. deaths) in sample.

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Cutaneous Kaposi Sarcoma Correlated with HHV-8 virus KSHV Infection Treated with Electrochemotherapy: A Single Institution Experience C. Caracò,* G. Di Monta, U. Marone, L. Benedetto, F. Buonaguro, M. Tornesello, N. Mozzillo. *national cancer institute, Naples, Italy.*

Background Electrochemotherapy (ECT) is a novel treatment that combines chemotherapy and electric pulses to enhance intracellular drug concentration to destroy cancer cells. Despite a routine clinical application of ECT in the treatment of melanoma cutaneous metastases, its role in Kaposi sarcoma is not well defined and literature reports are scarce. Aim of this study is to evaluate the efficacy of ECT in treatment of cutaneous Kaposi sarcoma, confirmed by the presence of the Human Herpes virus (HHV-8) antibodies in the serum and HHV-8-DNA in the specimen. Methods From January 2010 to June 2012 at National Cancer Institute of Naples, 22 patients with Kaposi sarcoma of the inferior limb, not amenable to surgery, radiotherapy or chemotherapy, were submitted to electrochemotherapy according European Standard Operating Procedures (ESOPE) guidelines. Each patient was submitted to surgical biopsy to analyze HHV-8 antigens and blood serum collection to test to antibodies anti HHV-8 positivity. Results A complete response to the first ECT session was obtained in 14(63.6%) patients. A second ECT was performed in 5(22.8%) cases and a third ECT in 3(13.6%). Overall the complete response was obtained in 17(77.2%) patients, while 5(22.8%) experienced a partial response. After a median follow-up of 16 months 16(72.7%) cases maintained the response and the overall survival rate was 100%. The presence of HHV-8 antigens in the specimens and serum antibodies anti HHV-8 was confirmed in all cases. Overall the treatment was well tolerated. Conclusions ECT is an effective treatment in Kaposi sarcoma of the lower limb and represents an additional tool in the management and local control of Kaposi cutaneous lesions. The presence of antibodies anti HHV-8 in the serum and the HHV-8 antigens in the specimens confirmed the correlation of this neoplasia with viral infection.

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Mesh Reconstruction of the Pelvis Following Internal Hemipelvectomy for Soft Tissue Sarcomas or Osseus Lesions of the Innominate Bone: Long Term Functional and Oncologic Outcomes in Thirty Patients N. Bloom,* S.S. Reddy. *Beth Israel Medical Center, New York, NY.*

Introduction: Between 1987 and 2010 thirty patients underwent an Internal Hemipelvectomy for tumors of osseus or soft tissue origin. All the patients were reconstructed with a polypropylene mesh only. Method: An internal hemipelvectomy was performed on eight patients with soft tissue tumors and twenty two patients with tumors arising from in the bone. Polypropylene mesh only was used to reestablish pelvic continuity and to reattach abvdominal and extremity musculature. Results: There was only one postoperative deep wound infection and one patient developed a superficial skin necrosis after receiving brachytherapy. No patients had any vascular or urologic complications nor were there any transient or permanent nerve damage other than in those patients whose femoral or obturator nerves were included in the resection of the soft tissue sarcomas. Utilizing the MSTS functional classification twenty eight patients had good or excellent results and two patients had fair results. Two patients developed incisional abdominal hernias more than four years after their initial operation. Of the thirty patients six patients developed a local recurrence. Four of the the six were reresected with easy access to the recurrent disease by dividing the mesh reconstructions. Four have died of disease and three are alive with disease. Conclusions: An internal hemipelvectomy can be incorporated in the en bloc resection for soft tissue tumors arising in the pelvis as well as from the innominate bone with little morbidity. Mesh reconstruction allows for pelvic stability good functional results easy access for recurrent disease and few late complications

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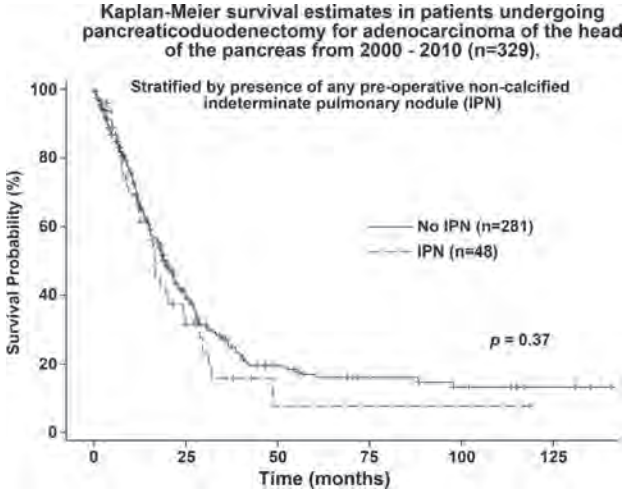
The Natural History of Pre-Operative Indeterminate Pulmonary Nodules in Patients with Resectable Pancreatic Adenocarcinoma D.C. Nguyen,* S. Chang, Z. Gongfu, A. Wang-Gillam, D.C. Linehan, W.G. Hawkins, S.M. Strasberg, C. Menias, C. Raptis, R.C. Fields. *Barnes-Jewish Hospital and the Alvin J. Siteman Cancer Center, Washington University, St Louis School of Medicine, St Louis, MO.*

Background: Pre-operative abdominal imaging often detects indeterminate pulmonary nodules (IPN) in patients with resectable pancreatic adenocarcinoma. The natural history of IPN in this setting is not well characterized. Methods: Patients with adenocarcinoma of the head of the pancreas who underwent resection (pancreaticoduodenectomy; PD) were queried from a prospectively maintained database. Pre- and post-operative imaging was reviewed and IPN characterized and analyzed for associations with nodule progression and overall survival (OS). Results: 463 patients underwent PD for adenocarcinoma of the head of the pancreas from 2000-2010. Of these, 329 (71%) had reviewable pre-operative imaging. 48 patients (15%) had pre-operative IPN (non-calcified) identified with follow-up imaging available for review. The only pre-operative factor associated with the presence of IPN was increasing age (68 v. 64 years; p=0.003). 8 patients (12%) had new or enlarging nodules, of whom 5 (7%) had confirmed pulmonary metastatic adenocarcinoma. There was no difference in OS between patients with or without pre-operative IPN (2-year OS 41% v. 38%, respectively; p=0.37; Figure). Further, no radiographic criteria of IPN (including # of, size of, bilateral, calcified, solid, spiculated, smooth, lobular, or ground-glass nodules) was associated with OS. On follow-up, new or enlarging nodules were not associated with OS. Conclusion: IPN are often found in patients undergoing resection for pancreatic adenocarcinoma. The majority of IPN remain stable on post-operative imaging. Neither the presence of IPN nor nodule characteristics was associated with OS. These data do not support the routine additional workup of pre-operative IPN in patients with resectable adenocarcinoma of the head of the pancreas; however, larger studies are needed to further characterize the significance of IPN (and the use of routine chest imaging in general) in the pre-operative evaluation of patients with pancreatic adenocarcinoma.



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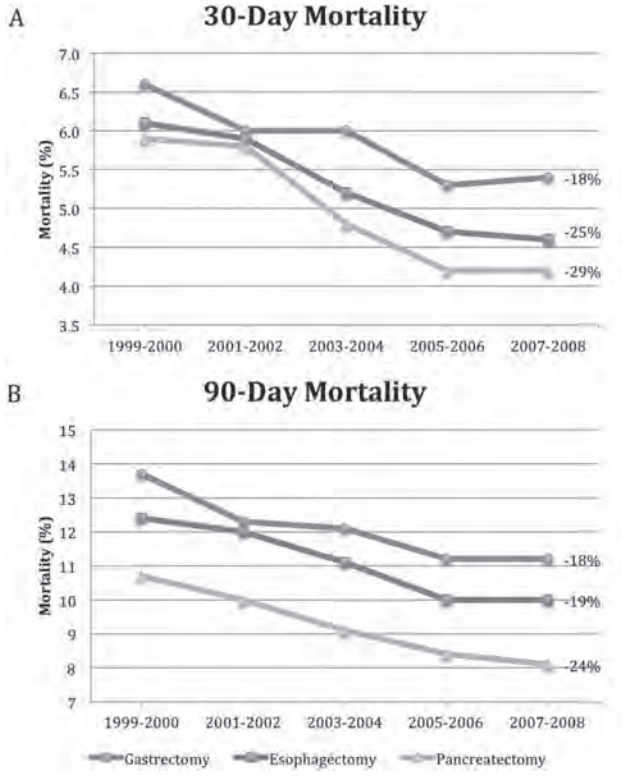
Is it as Safe and Easy as We Think? A Significant Opportunity to Improve Operative Mortality after Gastrectomy R.T. Williams,[1]* B.E. Palis,[2] K. Mallin,[2] A. Stewart,[2] R.P. Merkow,[2] M.S. Talamonti,[3] D.P. Winchester,[3] M. Posner.[1] *1. Surgery, University of Chicago, Chicago, IL; 2. American College of Surgeons, Chicago, IL; 3. NorthShore University HealthSystem, Evanston, IL.*

Background: While inverse volume-outcome relationships for esophagectomy (E) and pancreatectomy (P) are well established, with several studies showing a decrease in mortality after regionalization, determinants of mortality after gastrectomy (G) remain controversial. This study examines trends in mortality and regionalization for G, E, and P and explores the relative importance of factors driving G mortality. Methods: Factors associated with 30- and 90-day mortality after G were determined for Stage I-III gastric cancer patients in the National Cancer Database from 1999-2008. Trends in mortality, case mix, and the proportion of patients treated in hospitals in the top 2 volume quintiles were examined for G, E and P. Hierarchical regression was used to identify independent predictors of mortality after G, accounting for correlation within hospitals. Results: Overall, 30-day mortality was 5.9% after G (n=40,238), 5.3% after E (n=32,465), and 4.8% after P (n=31,495). 90-day mortality after G was 12.1%. Factors associated with the highest 90-day mortality post-G were age ≥ 80 (21.3%) and comorbidity score ≥ 3 (23.4%). Operative mortality decreased over time for all 3 procedures, but the relative decline was least for G (Figure). High volume hospitals treated an increased proportion of patients for all 3 surgeries (38% in 1999-2000 to 43% in 2007-2008 for G, 33% to 45% for E, 31% to 44% for P, p<0.001). More patients undergoing G were elderly (21.2% age ≥ 80 vs. 6.3% and 8.3% for E and P respectively) and had ≥3 comorbidities (2.3% for G vs. 1.2% for E, and 1.5% for P). The strongest independent predictor of mortality post-G was age ≥ 80 (OR 10.83, 95% CI 7.10-16.52). Conclusions: Trends in regionalization over time for G lag behind E and P. The more frequent performance of G in elderly and sicker patients has resulted in notably higher mortality rates for G relative to E and P. 90-day mortality was twice the 30-day mortality rate, suggesting 90-day mortality may be a more sensitive indicator of outcome post-G. These findings highlight ample opportunities to improve operative mortality for surgically treated gastric cancer patients in the U.S.



Temporal Trends in Operative Mortality for Gastrectomy, Esophagectomy, and Pancreatectomy

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Robotic Assisted Ivor Lewis Esophagectomy with or without Neoadjuvant Chemoradiation Therapy for Esophageal Cancer F. Smith,* K. Almhanna, S. Hoffe, R. Shridhar, R. Karl, K. Meredith. *H Lee Moffit Cancer Center, Tampa, FL.*

Background: Neoadjuvant chemoradiation therapy (NT) has become standard of care for patients with locally advanced esophageal cancer. In selected patients, robotic assisted Ivor Lewis Esophagectomy (RAIL) is a safe and feasible operative strategy in the management of esophageal cancer. This study was designed to determine potential differences in peri-operative morbidity and short term outcomes in patients with esophageal cancer treated with robotic assisted Ivor Lewis Esophagectomy with or without NT. Methods: A retrospective review of consecutive patients with esophageal cancer who underwent RAIL esophagectomy between October 2010 and June 2012 with and without NT was performed. Clinical and pathological variables were analyzed with two-sided student t-test assuming equal variance. Data were considered significant at a p-value <0.05. Results: Eighty-nine patients underwent RAIL during the study period. Seventy-seven patients (87%) received NT and twenty-two patients did not (13%). The median age was 66 years and the median BMI was 28 kg/m2. All patients had a R0 resection. There were no differences in the mean estimated blood loss (149 vs.153 mL; p = 0.52) and mean operative times (434 vs. 427 minutes; p = 1.0). There were no differences in the incidence of pneumonia or atrial fibrillation, lengths of stay in the ICU, or length of hospitalization. In total, there were two anastomotic leaks and one leak from the gastric conduit. The anastomotic leaks occurred in the group that did not receive NT and the gastric conduit leak occurred in the group that received NT. There were no mortalities in either group. There was no difference in the mean number of lymph nodes harvested in the NT group (22 ± 11 vs. 20 ± 8, p = 0.41). Conclusions: Robotic assisted Ivor Lewis Esophagectomy can be safely performed following neoadjuvant chemoradiation therapy. In this series there were similar perioperative, morbidity and short-term mortality outcomes in patients who received NT compared with robotic assisted Ivor Lewis alone. Longer follow-up is required in order to determine long term oncologic outcome.

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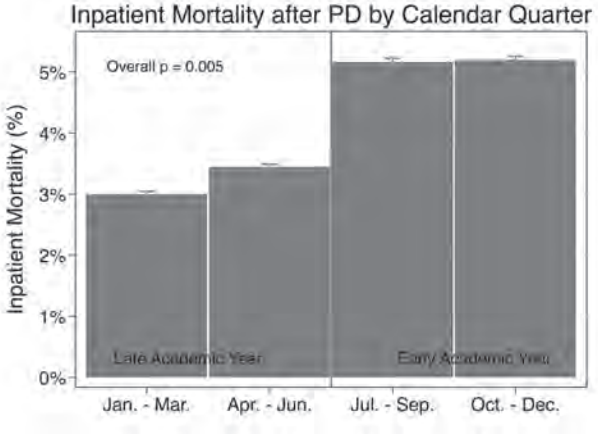
Inpatient Mortality after Pancreaticoduodenectomy for Cancer Decreases in the Latter Half of the Academic Year E.S. Glazer,* A. Amini, T. Jie, R.W. Gruessner, R.S. Krouse, E.S. Ong. *The University of Arizona, Tucson, AZ.*

Introduction: While operative and peri-operative mortality after pancreaticoduodenectomy (PD) continues to decrease, key factors remain to be elucidated. The Nationwide Inpatient Sample (NIS) is an inpatient database representing 20% of hospitalizations in the USA. The purpose of this study was to investigate inpatient mortality after PD for the two most recent years. Methods: Patient discharge data (ICD-9 diagnostic and procedure codes) and hospital characteristics were culled from the NIS 2009 & 2010 databases. The inclusion criteria were a PD procedure code and a pancreatic or peri-pancreatic cancer diagnosis. $\chi 2$ determined statistical significance. A logistic regression model for mortality was created from significant variables ($p < 0.05$). Results: Of the 2,958 patients who underwent PD with complete data, the average age was 65 ± 12 years; 53% were male. The mean length of stay was 15 ± 12 days with an inpatient mortality of 4% and a complication rate of 57%. 86% of PD occurred in teaching hospitals and were associated with non-significantly decreased mortality compared to non-teaching hospitals (4% vs 6%, $p = 0.10$). PD performed in teaching hospitals in the first half of the academic year were associated with a higher mortality than in the latter half (5.5% vs 3.4%, $p = 0.005$, figure). Private insurance was associated with lower mortality (3.0% vs 5.3%, $p = 0.02$) but household income, rural location, and hospital size were not related to mortality ($p > 0.3$). On logistic regression analysis, procedures in the latter half of the academic year remained protective of death (OR: 0.6, 95%CI: 0.4 to 0.8, $p = 0.004$) despite maintaining patient age, length of stay, and operative complications in the model (each $p < 0.001$). Conclusions: The timing of PD remained more predictive of mortality than age or length of stay; only complications were more predictive of death than time of year. This suggests that there remains a clinically and statistically significant learning curve for trainees. Since the majority of these procedures occur in teaching hospitals, the current restrictions on trainee education may directly affect mortality after PD.



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Iontophoretic Delivery of Gemcitabine is More Effective Than Systemic Gemcitabine in Pancreatic Cancer M. Jajja,* A. O'Neill, J. Byrne, R.E. Little, M.E. Napier, J.M. DeSimone, J. Yeh. *University Of North Carolina, Chapel Hill, NC.*

Introduction: More than 30% of patients with pancreatic ductal adenocarcinoma (PDAC) are nonmetastatic but unresectable at the time of diagnosis. Few patients respond to neoadjuvant chemotherapy sufficiently to become operative candidates. In PDAC there is convincing evidence that stromal fibrosis is a significant barrier to effective drug delivery. Using the principles of iontophoresis an electric field assisted device (EFAD) which transports drug by generating a charge gradient was developed to improve drug delivery in PDAC. Methods: EFAD delivery of 40mg/mL gemcitabine using 1-2mA for 10 minutes (EFAD-G) was compared to intravenous 80mg/kg gemcitabine (IV-G) in orthotopic PDAC patient-derived xenografts (PDX). Gemcitabine and its inactivated metabolite difluorodeoxyuridine (dFdU) was measured using high-performance liquid chromatography. Tumor response was evaluated at 3-6 weeks post-treatment using high-resolution ultrasonography. Results: Gemcitabine accumulation in tumors 30 minutes after EFAD-G was 109.3 ±23.0ug (n=10) compared to only 8.7 ±7.7ug (n=4) after IV-G, ($p<0.001$). Tumor growth inhibition (TGI) was seen as early as 3 weeks with EFAD-G. In a PDX that does not respond (NR) to gemcitabine (Fig. 1a) EFAD-G resulted in greater TGI with a log2 relative increase in tumor volume (TV) of +0.93 ±0.22 (n=5) compared to +1.98 ±0.31 (n=3) with IV-G, ($p=0.01$). Substantial tumor regression was seen at 6 weeks using EFAD-G with a log2 relative decrease in TV of -0.53 ±0.37 (n=3) (Fig. 1b) and -1.51 ±0.51 (n=2) compared to only -0.23 ±0.18 (n=5), ($p=0.26$) and -0.37 ±0.42 (n=8), ($p=0.03$) decrease with systemic delivery in two PDAC PDX responsive (R) to gemcitabine. Conclusion: EFAD delivery of gemcitabine results in better drug penetration in PDAC with an improved tumor response in both gemcitabine R and NR tumors without systemic toxicity. For patients with locally advanced unresectable PDAC, neoadjuvant therapy using EFAD delivery may be promising. For patients with local symptoms, EFAD delivery of chemotherapeutics may be more effective for palliation. EFADs are being developed for use in patients and should be evaluated in clinical trials for PDAC.

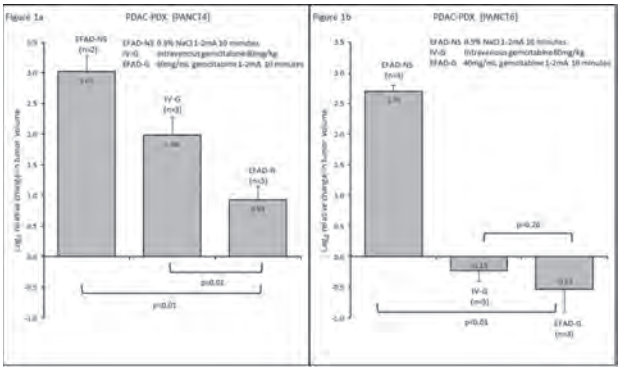

Figure 1. PDAC-PDX response to EFAD-G

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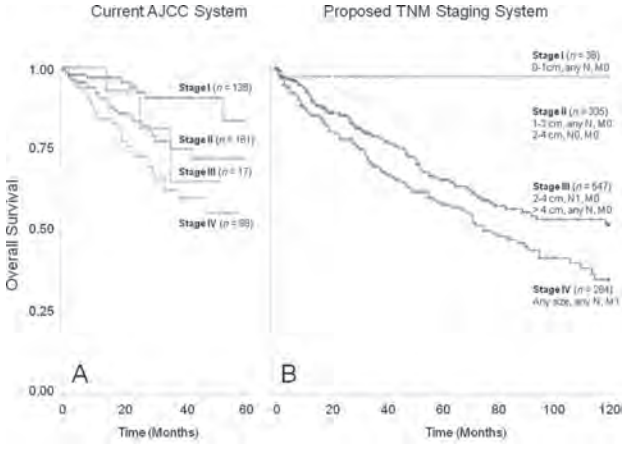
A Novel TNM Staging System for Pancreatic Neuroendocrine Tumors Outperforms the Current AJCC Staging System M. Qadan,* Y. Ma, B.C. Visser, J.A. Norton, G.A. Poultsides. *Department of Surgery, Stanford University Medical Center, Stanford, CA.*

Objective: Adopting a unified staging system for Pancreatic Neuroendocrine Tumors (PNET) has been challenging due to the rarity and heterogeneity of the disease. Currently, the American Joint Committee on Cancer (AJCC) recommends the use of the pancreatic adenocarcinoma staging system for PNET. We sought to validate this recommendation on a large administrative population database. Methods: Surveillance Epidemiology and End Results (SEER) data were used to identify patients with PNET (excluding patients with large cell, small cell, or mixed endocrine-exocrine carcinoma) who underwent curative-intent surgical resection from 1983 to 2008. The discriminatory ability of the AJCC system (recorded by SEER since 2004) was examined and a new TNM system was devised utilizing extent of disease variables. Results: Of 1,202 patients identified, 51% were female. Median age was 55 years (range, 9-93). Lymph node metastasis (present in 43% of patients) was associated with worse overall survival after resection (10 year, 50% vs 63%, $P < .0001$). Similarly, the presence of distant metastasis (present in 24% of patients) was associated with worse overall survival (10 year, 35% vs 63%, $P < .0001$).The current AJCC system (recorded in 412 patients) distinguished overall survival adequately only between stages I and II ($P = .01$), but not between II and III ($P = .97$), or III and IV ($P = .36$; Figure 1A). By modifying the T stage to be based only on size (0-1 cm, 1-2 cm, 2-4 cm and > 4 cm) and revising the grouping allocation, we propose a novel TNM system with improved discriminatory ability (stage I vs II, $P = .16$; II vs III, $P < .0001$; III vs IV, $P = .008$, Figure 1B). Conclusion: In this study validating the current AJCC staging system for PNET, we found stages II, III, and IV to perform similarly. We propose a novel TNM system that better discriminates between outcomes after surgical resection of PNET.



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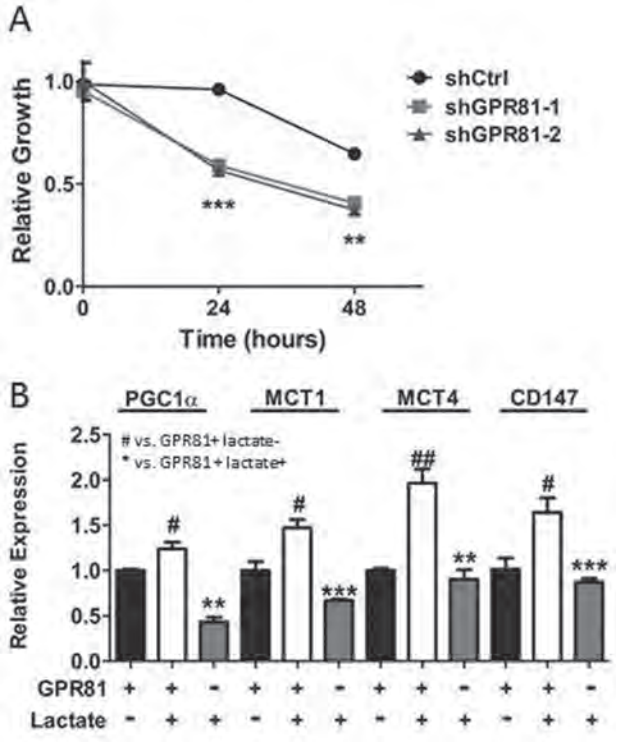
The Lactate Receptor, GPR81, is Critical for Pancreatic Cancer Cell Survival in the Tumor Microenvironment C.L. Roland,* T. Arumugam, D. Deng, V. Ramachandran, S. Liu, Z. Cruz-Monserrate, C. Logsdon. *MD Anderson Cancer Center, Houston, TX.*

Introduction: The increased energy demands required for the chronic and uncontrolled proliferation of malignant cells demands alterations in normal metabolism. Lactate, which is produced in large excess in tumors, also constitutes an alternative metabolic fuel for cancer cells in conditions of hypoxia or low glucose. GPR81 has recently been identified as the receptor for lactate and is mainly expressed by adipocytes. We have identified GPR81 expression in human pancreatic cancer cells. However, the role of GPR81 in pancreatic cancer (PDAC) has yet to be elucidated. Methods and Results: GPR81 is expressed by 93% of human PDAC samples by immunohistochemistry. To investigate the function of GPR81, stable knockdown of GPR81 was performed using short-hairpin RNA against GPR81 (shGPR81) or control (shControl). Cells were grown in media lacking glucose + 20mM lactate, to simulate the tumor microenvironment. At 24 hours, 44% of shGPR81 knockdown cells underwent cell death compared to 4% of control cells (Fig. 1A; $p<0.001$). To investigate the mechanism behind the inability of shGPR81 cells to survive, we performed quantitative PCR of the lactate transporters (MCTs) essential for the transport of lactate across cancer cell plasma membranes (Fig.1B). In the presence of lactate, shControl cells up-regulated the expression of MCT1, MCT4 and CD147 via expression of the co-transcription factor, PGC1α, a known regulator of MCTs. However, shGPR81 cells had reduced levels of lactate transporters and were unable to increase the expression of MCTs. Furthermore, lentiviral overexpression of GPR81 in GPR81-low MPanc96 cells promoted cell survival, whereby at 72 hours, 113% of GPR81-overexpressing cells were alive, compared with 26% of GPR81-low cells ($p<0.001$). These data indicate that GPR81 is necessary for increased MCT expression required for cell survival in the presence of lactate. Conclusions: GPR81 expression by PDAC cells regulates the expression of MCTs, which are necessary for tumor cell survival in the lactate-rich tumor microenvironment. These results suggest that targeted therapy inhibiting GPR81 could provide a novel approach to PDAC therapy.



shControl: black and white bars; shGPR81: red bars

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Hybrid Endoscopic and Laparoscopic Resection of Metastatic Renal Cell Carcinoma to the Gastric Mucosa F.G. Rocha,* C. Williams, A. Ross. *Surgery, Virginia Mason Medical Center, Seattle, WA.*

Background: Renal cell carcinoma (RCC) has a propensity to spread to distant metastatic sites including the gasotrintestinal tract; however, isolated gastric mucosal metastasis is rare. There are 36 cases reported in the English literature. We present the case of a 62yM with a history of a remotely resected T2N0 renal cell carcinoma who presented with iron deficiency anemia and was found to have a biopsy-proven RCC metastasis to his gastric mucosa. He underwent a full staging work-up including CT, PET and bone scan and this was revealed to be the only site of disease. Purpose: To describe a novel hybrid approach to gastric resection combining the advantages of endoscopic and laparoscopic techniques for difficult lesions to remove by either approach individually. Description: Patient was taken to the operating room and laparoscopic exploration did not reveal evidence of disseminated disease. Given the small size and mucosal location of the lesion, it could be visualized externally. Esophagogastroduodenoscopy was performed intraoperatively and the lesion identified. Given its flat morphology, the lesion could not be easily snared by the endoscope until the gastric wall was "pushed" externallyby a laparoscopic instrument. Once resected endoscopically, the lesion was sent for frozen section analysis, however the deep margin could not be cleared of tumor presence with certainty. An endoscopic wire was then used to "push" the gastric mucosa internally so that it could be grasped by the laparoscopic instruments. A gastric wedge resection was performed using a laparoscopic stapler. Final pathology revealed a 7mm focus of metastatic renal cell carcinoma in the antral mucosa with overlying ulceration. Although the deep margin of the mucosal resection was positive, there was no additional tumor in the wedge resection. Patient was discharged on postoperative day #2 and remains disease-free.

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Circulating Tumor Cells as a Possible Marker for Micrometastatic Disease in Patients with Localized Pancreatic Cancer

R.D. Aufforth,[1]* J.J. Baker,[2] M.A. Witek,[3] J.W. Kamande,[3] H.J. Kim,[1] P. Kuan,[4] S.A. Soper,[3] J. Yeh.[1] *1. University of North Carolina School of Medicine, Division of Surgical Oncology and Endocrine Surgery, Chapel Hill, NC; 2. Maine Medical Center, Portland, ME; 3. University of North Carolina Department of Biomedical Engineering, Chapel Hill, NC; 4. University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC.*

Bachground: Circulating tumor cells (CTCs) are cells shed into circulation from tumors. They are increasingly recognized to be important biomarkers of disease burden in patients with solid tumors. Studies in pancreatic ductal adenocarcinoma (PDAC) have been limited due in part to low sensitivity of existing assays with extremely low numbers detected (0-15 per 7.5-15ml of blood). The development of newer microfluidic platforms has resulted in the ability to detect substantially greater numbers of CTCs. Methods: 15 patients with PDAC were enrolled in an IRB-approved study. Blood was collected in EDTA tubes and processed within 3 hours. CTCs were selected from 2-3ml of whole blood using monoclonal antibodies against epithelial cell adhesion molecule (EpCAM) and enumerated using a novel microfluidic platform. CTCs were confirmed by DAPI, CK8/18/19 and CD45 staining. Results: Patients with metastatic disease (n=12) had a mean of 29.7, median of 22 (3.5-107) CTCs per 1ml of blood. Patients with localized disease (n=3) had a mean of 3.8, median of 2.9 (2.3-6.2) CTCs per 1ml of blood. 0.5-1 CTCs per 1ml were detected in normal controls (n=2). The number of CTCs was significantly different between localized, metastatic and normal patients (p=0.01). 1 patient, initially thought to have localized disease by standard imaging but found to be metastatic at time of operation, had a mean of 45.9 CTCs per 1ml of blood compared to a mean of 3.8 CTCs per 1ml in patients who underwent a curative resection (p=0.009). Conclusions: Studies of CTCs in PDAC have been very limited. Our ability to detect large numbers of CTCs with good dynamic range suggests that further investigation into CTCs as a prognostic marker in PDAC is warranted. This is the first study that we are aware of to find CTCs in patients with localized disease. The presence of CTCs in patients with localized PDAC is surprising and may be associated with findings of unexpected metastatic disease at surgery. Further follow-up will be needed to determine if the presence of CTCs in these patients is a harbinger of shorter progression-free survival and overall survival after curative operations.

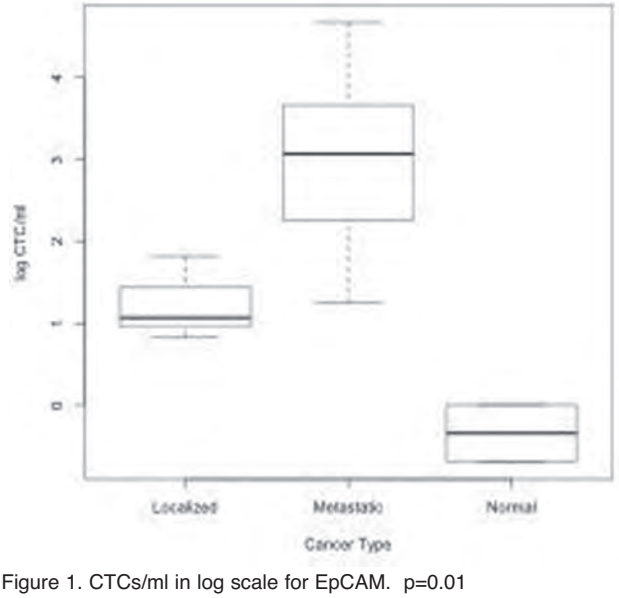

Figure 1. CTCs/ml in log scale for EpCAM. p=0.01

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Monocyte Prevalence Predicts Survival in Pancreas Cancer

D.E. Sanford,* R.Z. Panni, B. Belt, D.G. Denardo, P. Goedegebuure, D.C. Linehan. *Washington University in St. Louis, St. Louis, MO.*

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense immune infiltrate which influences tumor progression. Monocytes/macrophages(Mo) are abundant within the tumor microenvironment. The CCL2-CCR2 chemokine axis is a crucial signaling pathway in physiologic Mo recruitment, and CCR2+ Mo may play an important role in cancer progression. Therefore, we hypothesized that peripheral blood Mo corelate with patient survival in PDAC. Methods: Flow cytometry was performed on the peripheral blood mononuclear cells (PBMC) of PDAC patients (n=13) and compared to healthy controls (n=11). PDAC tumor specimens (n=11) and normal pancreas (n=8) were subjected to flow cytometry and RT-PCR. 483 patients with PDAC underwent pancreaticoduodenectomy between 1997 and 2011 at a single institution. We stratified patients into 3 groups based on the prevalence of Mo in peripheral blood leukocytes using their pre-op CBC: low(<6%), mid(≥6% to <11%), and high(≥11%) Mo groups. We exluded all patients with elevated pre-op leukocytosis (WBC>11,000 cell/ul) and those who died within 30 days of surgery. We used standard Kaplan Meier survival statistics on this cohort of 373 patients to compare overall survival between the three groups. Results: CCR2+ Mo were significantly more prevalent in the PBMC of PDAC patients compared to controls (10.8% vs 5.7% of CD45+ cells; p<0.005 - Fig 1A). PDAC tumors express significantly more CCL2 relative to normal pancreas(p<0.01) and these tumors are infiltrated by CCR2+ Mo (37.9% ±1.6% of CD45+ cells). PDAC patients in the low Mo group survived significantly longer than patients in the high Mo group; p=0.02(log-rank test). The median survival in the low Mo group was 27.8 months compared to 18.2 months in the high Mo group. Also, there was a statistically significant decrease in survival from the low to mid to high Mo groups; p=0.01 (log-rank test for trend) - Fig 1B. Conclusion: Mo are recruited to the tumor microenvironement in PDAC through the CCL2/CCR2 chemokine axis, and the prevalence of peripheral blood Mo corelates with decreased patient survival. Developing effective intevention strategies to thwart Mo recruitment may hold significant promise in this disease.

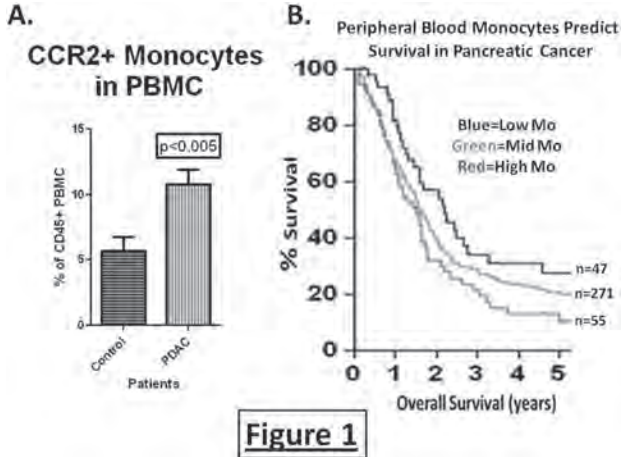

Figure 1

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FAK-VEGFR3 Signaling is a Promising Target for the Development of Novel Therapeutics in Gastric Cancer E.V. Kurenova, J. Liao, T.A. Platz, W. Cance, S.S. Sanghera.* *Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: Focal Adhesion Kinase (FAK) is an emerging target for developmental therapeutics in cancer. FAK acts as a survival signal for cancer cells, working both as a kinase and as a scaffolding protein to regulate the interaction of multiple downstream signaling proteins. We have developed a compound, C4, which targets the scaffolding function of FAK. This drug specifically inhibits the interaction of FAK with Vascular Endothelial Growth Factor Receptor – 3(VEGFR3). Both of these kinases are found to be expressed at high levels in human gastric cancer specimens. We hypothesized that inhibition of FAK-VEGFR-3 interaction with C4 would inhibit cellular proliferation and induce apoptosis. Methods: FAK and VEGFR3 over-expression in human cancer cell lines AGS and NCI-N87 was determined by Western Blotting (WB). WB was then used to confirm decreased levels of phosphorylated FAK after treatment with the compound C4. Cells maintained in monolayer were treated overnight with incremental doses of the drug and then MTT assay was performed to test for inhibition of cell viability. Similarly, Colony Forming Assay

was performed to demonstrate the effect of the drug on cellular proliferation. Results: FAK and VEGFR-3 were found to be over-expressed in human gastric cancer cell lines as determined by WB. The drug C4 specifically blocked phosphorylation of FAK at its major autophosphorylation site, Tyrosine 397 (Y397). Inhibition of the phosphorylated form of VEGFR3 was also evident. As predicted, compound C4 directly and significantly ($p<0.05$) inhibited cell viability in a dose dependent manner (range 1-100μM) as demonstrated by MTT assays in both cell lines tested (Fig 1A and 1B). Moreover, colony forming assays demonstrated a significant ($p<0.05$) inhibition of cellular proliferation after 8 days of treatment with the drug. Conclusions: These data suggest that the FAK-VEGFR-3 signaling axis is an important component in human gastric cancer survival mechanisms and that inhibition of this pathway may offer a novel approach for the treatment of gastric cancer.

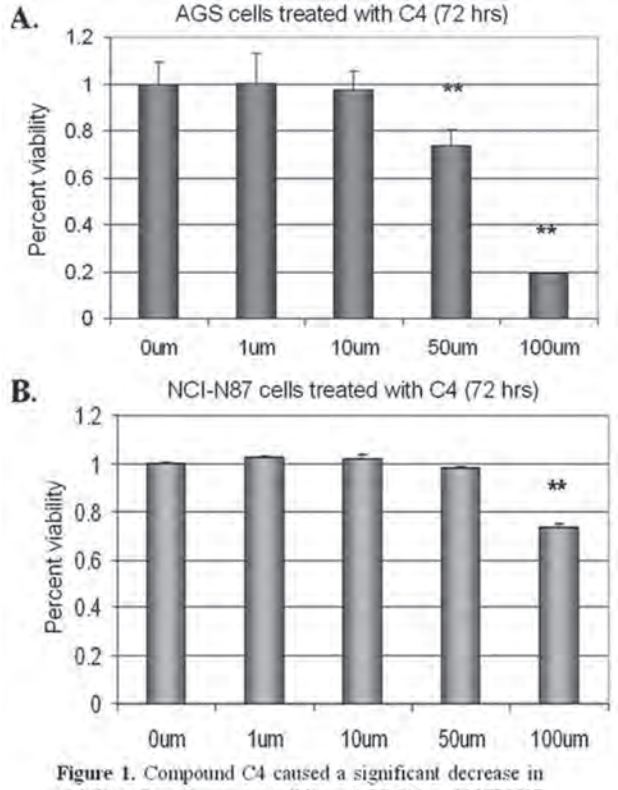

Figure 1. Compound C4 caused a significant decrease in viability of gastric cancer cell lines AGS (A) and NCI-N87 (B) in a dose-dependent manner.

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Outcomes of Pancreaticoduodenectomy in Octogenarians, an ACS-NSQIP Analysis D.Y. Lee,* J.A. Schwartz, D. Kirchoff, B.A. Wexelman, C.K. Yang, F. Attiyeh. *Surgery, St. Luke's Roosevelt Hospital Center, New York, NY.*

Introduction- Most series analyzing the outcomes of pancreaticoduodenectomy in octogenarians are limited by a small sample size. We used the ACS-NSQIP database for an analysis of advanced age on outcomes after elective pancreatic cancer surgeries. Methods- The ACS-NSQIP Participant User File (PUF) from 2005-2010 was used to study outcomes of 487 pancreaticoduodenectomies performed in patients ≥ 80 years (mean 82.8 ± 2.6). Their outcomes were compared to 4,188 patients < 80 years (mean 63.7 ± 10.2). A stepwise multivariate binomial logistic regression to analyze factors associated with 30-day mortality. Results- Patients ≥ 80 years had a significantly higher ASA class, more cardiovascular, pulmonary, and central nervous system comorbidities. The mortality rate of patients ≥ 80 was 6.4% (31/487) compared to 2.5% (103/4,188) for patients < 80 years (p=0.0001). On multivariate analysis, patients < 70 years was associated with increased odds ratio of survival (Table 1). However, patients ≥ 80 years was not associated with increased mortality compared to those between the ages of 70-79 (OR 1.5, 95% [CI]: 0.9-2.4, p=NS). Additional factors associated with mortality include: dependent functional status, hypertension, dyspnea on rest, chronic steroid use, history of peripheral vascular disease and ascites. Major complications occurred in 21% (102/487) of patients < 80 compared to 15% (641/4,188) for those ≥ 80 years (p = 0.001). BMI (kg/m2) >35, HCT (%)< 30, PT>20 seconds, history of disseminated cancer, myocardial infarction, percutaneous cardiac intervention, peripheral vascular disease, COPD, dyspnea on exertion, and functional dependence were all associated with the occurrence of complications. Age ≥ 80 was not an independent risk factor for developing major complications. Conclusion- Although the rate of complications and mortality was higher in patients ≥ 80 years, this cohort did not have a significant increased complication rate or morbidity compared to patients 70-79 years. Additional preoperative factors predictive of mortality were unveiled which can aid surgeons in selecting the most appropriate candidates for pancreatic cancer resections.

Table 1- Multivariate analysis of preoperative factors associated with 30 day-mortality

Prognostic Factors	Adjusted OR (95% CI)	p Value
Age		
<70 years	Referent	
70-79 years	2.1 (1.4-3.1)	0.001
≥80 years	3.0 (1.9-4.9)	<0.0001
Independent Functional Status	Referent	
Partially Dependent	2.8 (1.5-5.1)	0.001
Totally Dependent	4.4 (1.2-16.9)	0.029
HTN (requiring medication)	1.6 (1.1-2.5)	0.017
No Dyspnea	Referent	
Dyspnea with Exertion	1.8 (1.1-3.0)	0.013
Dyspnea on Rest	7.8 (2.4-24.6)	0.001
Chronic Steroid Use (Yes)	2.3 (1.0-5.3)	0.042
History of PVD (Yes)	2.9 (1.2-15.4)	0.001
Radiation	2.0 (1.0-4.1)	0.062
Ascites (Yes)	5.5 (1.9-15.4)	0.001

HTN= Hypertension; PVD= Peripheral Vascular Disease

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Different Recurrence Pattern after Neoadjuvant Chemoradiotherapy Compared to Surgery Alone in Esophageal Cancer Patients J.K. Smit,* S. Guler, J.C. Beukema, V.E. Mul, J.G. Burgerhof, G.A. Hospers, J.T. Plukker. *University of Groningen, University Medical Center, Departments of Surgical Oncology, Radiation Oncology, Medical Oncology and Epidemiology, Groningen, Netherlands.*

Introduction: Neoadjuvant chemoradiotherapy (CRT) is currently considered standard treatment in esophageal cancer patients who are eligible for surgical resection with curative intent. Objective was to evaluate the recurrence pattern after neoadjuvant CRT in patients with esophageal cancer. Methods: We analyzed the results and recurrence patterns from a single center (N=152) in a propensity score matched study between patients treated with neoadjuvant CRT (N=44) and surgery alone (44 from the 108),in the period 2002-2010. Patients treated with neoadjuvant (CROSS schedule) carboplatin/paclitaxel and 41.4 Gy radiotherapy, were compared with a historical cohort of patients with curative intended surgery alone. Results: After matching, the baseline characteristics were equally distributed between both groups (table 1). The response to CRT was 63%, with a pathological complete response of 26%. After a median follow-up of 23 months (7-74 months), lung was the most common site of distant recurrence (16%, N=7), followed by distant lymph nodes (11%, N=5) in the neoadjuvant CRT group, whereas skeletal metastases were the most common site of distant recurrence (18%, N=8), followed by skin or soft tissue (16%, N=7) in the surgical alone group. The estimated 3 and 5 year overall survival was 62% and 55% in the neoadjuvant CRT group, compared to 37% and 31% in the surgery group (Log-rank test: P=0.018). The estimated locoregional free recurrence survival (LRFS) after 3 and 5 years

was 79% and 68% in the neoadjuvant CRT group, compared to 44% and 40% in the surgery alone group (Log-rank test: P=0.049). The estimated distant recurrence free survival (DRFS) was 63% and 54% after 3 and 5 years in the neoadjuvant CRT group, compared to 50% and 35% in the surgery alone group (Log-rank test: P=0.314). Conclusions: This neoadjuvant CRT regimen significantly improved the oncological outcome compared to surgery alone. An important shift in the recurrence pattern was observed from relatively high locoregional recurrences (LRFS) to relatively more distant recurrences (DRFS) in the CRT group compared to the surgery alone group.

Table1: Baseline characteristics after propensity score matching

Characteristics	Neoadjuvant CRT N=44	Surgery alone N=44	P value
Age (mean)	59.8 (38-74)	60.6 (44-71)	0.635
Sex male female	 73% (N=32) 27% (N=19)	 80% (N=35) 20% (N=9)	0.618
Histology AC SCC	 82% (N=36) 18% (N=8)	 84% (N=38) 14% (N=6)	0.772
cT-stage cT1 cT2 cT3 cT4	 0% (N=0) 18% (N=8) 77% (N=34) 5% (N=2)	 0% (N=0) 14% (N=6) 80% (N=35) 7% (N=3)	0.779
cN1	75% (N=33)	80% (N=35)	0.800
Localization Mid Distal GEJ	 7% (N=3) 82% (N=36) 11% (N=5)	 9% (N=4) 75% (N=33) 16% (N=7)	0.738

GEJ= gastroesophageal junction, AC=adenocarcinoma, SCC=squamouscellcarcinoma

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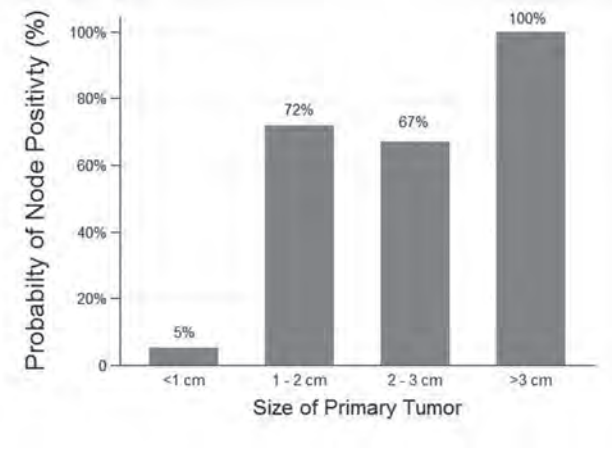
Duodenal and Ampullary Carcinoid Tumors: Size Predicts Necessity for Lymphadenectomy E. Dogeas,* I. Hatzaras, J.L. Cameron, C. Wolfgang, K. Hirose, R.H. Hruban, M.A. Makary, T. Pawlik, M.A. Choti. *Surgery, Johns Hopkins School of Medicine, Baltimore, MD.*

Introduction: The metastatic potential and choice of therapy of duodenal and ampullary carcinoid tumors are poorly understood. We evaluated the local management and outcomes in patients with these uncommon tumors and determined factors predicting risk of nodal involvement. Methods: 117 patients were identified with duodenal or ampullary carcinoid tumors between 1996 and 2012, who were treated in a single high-volume center. Clinicopathologic data and overall survival by local treatment modality were analyzed. Results: Among all patients, 64 (55%) were treated surgically, including 34 (29%) who underwent pancreaticoduodenectomy (PD) for the disease, 14 (12%) who underwent local resection (partial duodenectomy), and 16 (13.6%) where a carcinoid tumor was found incidentally after PD for another indication. The remaining 53 patients (45%) underwent endoscopic excision. The average tumor size was 1.8 cm (0.1-8.5) and the majority were of duodenal origin (n=93, 80%). Surgical management was more commonly performed for ampullary tumors compared to tumors of duodenal origin (83% vs. 47%, p=0.002), and endoscopic excision was more common with smaller tumors (p=0.001). Most carcinoids were well-differentiated (94%) and 55% were T1/T2. Yet, among the 55 patients in whom lymph nodes were histologically assessed (PD or lymph node sampling), 51% had positive nodes (N+). In addition, on multivariate analysis nodal involvement was strongly associated with tumor size (OR: 9.9, p=0.001). Specifically, tumors larger than 1-cm had positive nodes in more than 70% of cases whereas those ≤1cm had a 5% risk of nodal involvement (1 of 21 patients) (figure). Similar rates of N+ were observed for both duodenal and ampullary carcinoids. With long-term follow-up, only one recurrence was observed (1%). The overall survival was similar among all treatment groups (median=139 months). Conclusion: Lymph node involvement is common in patients with duodenal and ampullary carcinoid tumor, particularly among tumors >1-cm in size. When possible, surgical resection with lymphadenectomy is recommended for such tumors.



P298

Minimal Differences in Biomarker Profiling of Resected Pancreatic Adenocarcinoma Between Patients Receiving Neoadjuvant Therapy and Those Treated with Surgery First C.H. Pilgrim,* A.F. Mahmoud, K.K. Christians, S.G. Pappas, K.K. Turaga, E. Quebbeman, T. Gamblin, B. George, B. Erickson, T. Kelly, P. Ritch, D. Evans, S. Tsai. *Surgical Oncology, Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Chemotherapeutic biomarkers from surgical specimens have been examined for their prognostic value in the adjuvant setting. The impact of neoadjuvant chemotherapy on patterns of biomarker expression has not been described. Methods: Specimens from patients with resectable pancreatic ductal adenocarcioma (PDAC) were sent to a commercial laboratory for chemotherapeutic profiling (CP) from 2009-present. CP defined agents as likely-beneficial, indeterminate, or non-beneficial based upon drug-associated gene expression. The effect of neoadjuvant therapy on CP and survival was examined. Results: Sixty-seven patients specimens were submitted, and 48 were deemed adequate for CP. Of the 48 study patients, 39 (79.6%) received neoadjuvant chemotherapy prior to CP and 10 (20.4%) had a surgery-first approach. No differences were observed in total number of predicted beneficial agents (7.2 vs. 7), number of beneficial agents received (0.6 vs. 1.1), or total number of agents received (2.2 vs. 2.6). No differences were observed in patterns of predicted beneficial agents between the groups (Table). Overall survival was not influenced by number of predicted effective agents identified nor predicted effective agents received. However, patients whose CP predicted benefit with gemcitabine or irinotecan demonstrated a non-significant trend towards improved overall survival. Conclusions: This initial study suggests neoadjuvant therapy does not influence biomarker expression pattern in resected PDAC specimens. Prospective clinical trials which utilize pre- and post-therapy biomarker profiling as a guide to treatment decision-making are needed to assess the predictive utility of these biomarkers.

Samples with CP predictive of benefit, X/Y* (%)

Drug	Neoadjuvant therapy	Surgery first	p value
Gemcitabine	3/8 (37.5)	2/4 (50)	NS
5-FU	31/31 (100)	6/6 (100	NS
Irinotecan	18/39 (46)	6/10 (60)	NS
Oxaliplatin	24/33 (73)	6/7 (86)	NS
Nab-paclitaxel	11/11 (100)	5/5 (100)	NS

* X=CP predicted to be of benefit, Y=total specimens with CP for that agent (excluding specimens that profiled as indeterminate)

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Preoperative Bowel Preparation for Pancreaticoduodenectomy: Is it Necessary? T.E. Newhook,* J.M. Lindberg, R.B. Adams, T.W. Bauer. *Department of Surgery, University of Virginia, Charlottesville, VA.*

Introduction: Preoperative bowel preparation (PBP) before pancreaticoduodenectomy (PD) is commonly performed, however the effect of PBP on intra-operative fluid requirements and post-operative renal function after PD has not been reported. The goal of this study was to determine the effect of PBP on postoperative complications, intra-operative fluid requirements, and

post-operative renal function after PD. **Methods:** In this retrospective sequential analysis, all patients undergoing PD consecutively from September 2005 to July 2012 by a single surgeon were identified. Clinical data from patients who received PBP from September 2005 to November 2008 was compared to those without PBP from December 2008 to July 2012. **Results:** In all, 140 consecutive patients were identified with 49 (35%) having received PBP. There was no significant difference in the frequency of current smokers, diabetics, or chronic renal failure patients between the two groups. The PBP group received a significantly larger total intra-operative fluid volume (9.33 vs 6.54, p<0.001) and had a higher incidence of post-operative acute renal failure (22.4% vs. 5.4%, p = 0.003) compared to those without PBP. There was no significant difference in the rates of superficial, deep, or organ space surgical infections between the groups with a mean maximum WBC increase from baseline of 8.5 for PBP versus 7.2 without PBP (p=0.23). Additionally, there was no significant difference in the rates of pancreatic leak, other GI tract leak, or post-operative ileus between the groups. **Conclusions:** Pre-operative bowel preparation is not associated with a significant reduction in surgical site infections. In contrast, it is associated with a 2.8 liter increase in intra-operative fluid administration and a 17% increase in the incidence of post-operative acute renal failure. Thus, PBP should not be offered routinely prior to pancreaticoduodenectomy.

Clinical Data for Patients Who Underwent Pancreaticoduodenectomy With or Without Pre-operative Bowel Preparation

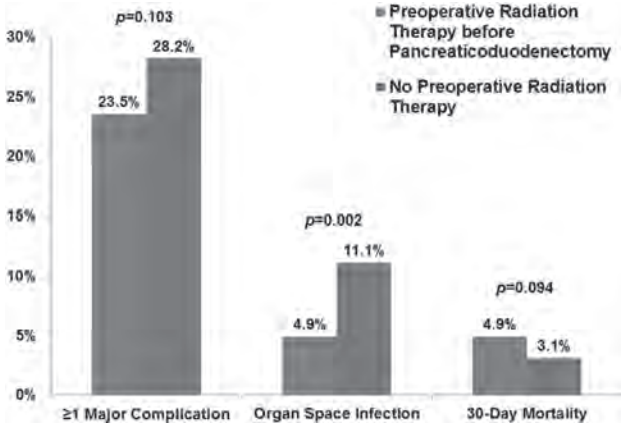
	Preoperative Bowel Preparation		
	Yes (n=49)	No (n=91)	*p* Value
Current Smoker	16 (32.6%)	23 (25.3%)	0.315[c]
Diabetic	14 (28.5%)	20 (21.9%)	0.349[c]
Chronic Renal Failure	0	0	1.000[c]
Total OR IV Fluids (L)	9.33 (0.24)	6.54 (0.58)	**<0.001**[d]
Pre-operative Creatinine (mg/dL)	0.95 (0.04)	0.91 (0.03)	0.442[d]
Maximum Change in Creatinine (mg/dL)	0.136 (0.04)	0.137 (0.03)	0.990[d]
Post-operative Acute Renal Failure	11 (22.4%)	5 (5.4%)	**0.003**[c]
Post-operative Respiratory Failure	0	1 (1.1%)	1.000[c]
SSSI	28 (57.1%)	39 (42.9%)	0.106[c]
DSSI	7 (14.3%)	12 (13.2%)	0.856[c]
OSSI	9 (18.4%)	13 (14.3%)	0.527[c]
Pre-operative WBC (x10^3/μL)	8.5 (1.28)	7.4 (0.28)	0.308[d]
Maximum WBC Change (x10^3/μL)	8.5 (1.20)	7.2 (0.52)	0.234[d]
Pancreatic Leak	2 (4.1%)	3 (3.3%)	1.000[c]
Other Leak	3 (6.1%)	5 (5.5%)	1.000[c]
Post-operative Ileus	3 (6.1%)	4 (4.4%)	0.659[c]

[a]Data presented as total counts (column percentage) or mean (SEM), [b]Chi-Square Test, [c]Fischer's Exact Test, [d]Independent Samples T-Test,
SSSI = Superficial Surgical Site Infection, DSSI = Deep Surgical Site Infection, OSSI = Organ Space Surgical Infection

P300

Morbidity and Mortality of Pancreaticoduodenectomy after Preoperative Radiation Therapy: A NSQIP Analysis C.D. Tzeng,* J.E. Lee, M.H. Katz, P.W. Pisters, J.B. Fleming, J. Vauthey, T.A. Aloia. *The University of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Because radiation therapy (RT) is uncommonly used before pancreaticoduodenectomy (PD), data on its impact on surgical outcomes is limited to single-institution reports. This study was designed to analyze the incidence of and risk factors for post-PD morbidity/mortality in a national cohort treated with preoperative RT. Methods: All elective PDs were evaluated in the 2005-10 ACS-NSQIP participant use file. Factors associated with 30-day rates of morbidity/mortality were compared in patients with/without RT ≤90 days before surgery. Major complications included organ injury, sepsis, re-operation, organ space infection, and venous thromboembolism. Results: Of 8,833 PDs, preoperative RT patients accounted for 243 (2.8%) cases. Compared to non-RT, RT patients were less likely to undergo surgery with preoperative hyperbilirubinemia (15.2% vs. 41.0%), leukocytosis (2.1% vs. 8.1%), BUN≥20mg/dL (7.0% vs. 18.5%), and elevated creatinine≥1.3mg/dL (3.7% vs. 8.8%) (all p≤0.006). Likewise, RT patients were less likely to be hospitalized immediately prior to PD (7.0% vs. 16.9%, p<0.001). Both cohorts experienced similar rates of major complications (23.5% RT vs. 28.2% non-RT, p=0.103), but organ space infections were less frequent (4.9% vs. 11.1%, p=0.002) after RT. Multivariate analysis identified the following risk factors for major complications: diabetes (odds ratio, OR-3.25, p=0.022), dyspnea (OR-6.38, p=0.034), AST >46 IU/L (OR-5.28, p=0.001), and intraoperative transfusion ≥4units (OR-6.26, p=0.003). Postoperative mortality was similar (12 events or 4.9% RT vs. 3.1% non-RT, p=0.094). Risk factors associated with mortality included AST >46 IU/L (p=0.010), hospitalization ≥1 day before surgery (p=0.042), intraoperative transfusion ≥4units (p=0.038), and operative time ≥420min (p=0.018). Conclusions: This analysis demonstrates that preoperative RT does not increase the risk of morbidity/mortality for PD patients. In addition, the lower rate of organ space infections in the RT group may reflect reduced rates of pancreatic leak. Concern for postoperative complications should not preclude surgeons from using preoperative RT when oncologically indicated.



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P301

Clinical Significance of PICT1/GLTSCR2 Expression in Gastric Cancer R. Uchi,[1]* R. Kogo,[2] H. Ueo,[1] Y. Takano,[1] T. Matsumura,[1] M. Ishibashi,[1] T. Sudo,[1] K. Sugimachi,[1] A. Suzuki,[3] S. Komune,[2] K. Mimori.[1] *1. Department of Surgery, Kyushu University Beppu Hospital, Beppu, Japan; 2. Department of Otolaryngology, Graduate School of Medical Sciences, Faculty of Medicine, Kyushu University, Fukuoka, Japan; 3. Division of Cancer Genetics, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan.*

Introduction: PICT1/GLTSCR2 is a nucleolar protein, which regulates MDM2-p53 pathway via its interaction with the ribosomal protein RPL 11. PICT1 expression levels were associated with a better prognosis in colorectal cancer and esophageal squamous cell carcinoma patients with wild-type p53 tumors. The current study aimed to investigate the expression of PICT1 and its function in gastric cancer. Methods:We evaluated p53 status and PICT1 expression levels in 110 gastric cancers and analyzed the association of PICT1 expression with clinicopathologic factors and prognosis. We downregulated PICT1 expression in gastric cancer cells with wild-type p53 using lentiviral-mediated RNAi. Results:Of 110 gastric cancer samples tested, 70 (63.6 %) and 40 (36.4 %) tumors had wild-type and mutant p53. We divided the two groups according to their PICT1 expression level (PICT1 high expression group: PICT1/GAPDH > 1, low expression group: PICT1/GAPDH < 1). In gastric cancer cases with wild-type p53 tumors (n = 70), the PICT1 high expression group (n = 35) had a poorer prognosis for overall survival as compared to the low expression group (n = 35, P = 0.046) However, for mutant p53 (n = 40) and total gastric cancer cases (n = 110), PICT1 expression levels did not correlate with overall survival. We also analyzed the association between PICT1 expression levels and clinicopathologic factors in gastric cancer patients with wild-type p53 tumors and found that PICT1 expression was significantly associated with tumor depth (P = 0.03). PICT1 knockdown in AGS cells, which has wild-type p53, induced p53 accumulation and upregulation of p21 and Bax, which are major p53 transcription targets. PICT1 knockdown decreased the proportion of cells in the S and G2/M phase as measured by a cell cycle assay, which indicates that PICT1 depletion induces G1 arrest. Conclusions: PICT1

should be a novel prognostic factor in gastric cancer patients with wild-type p53 tumors. PICT1 knockdown significantly impaired cell proliferation and colony formation via p53-mediated cell cycle arrest.

P302

Kinesin 18A Expression Clinical Relevance to Gastric Cancer
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Kif18A, a member of the kinesin superfamily of molecular motor proteins, is a microtubule depolymerase and a key regulator of chromosome congregation. Kif18A's role in cancer progression has not been well defined. Our hypothesis is that Kif18A has a role in the progression of gastric cancer. To investigate this expression of Kif18A, mRNA was assessed by qRT-PCR in 100 operative specimens of primary gastric cancer. Kif18A was overexpressed and significantly ($P < 0.0001$) higher in gastric cancer than in normal gastric tissue. Kif18A overexpression in gastric cancer significantly correlated with clinicopathologic factors such as lymphatic invasion ($P = 0.001$), lymph node metastasis ($P = 0.01$), venous invasion ($P = 0.002$) and peritoneal dissemination ($P = 0.02$), suggesting it has a key role in gastric cancer progression. In multivariate analysis, high Kif18A expression had independent significance for poorer overall survival after resection of gastric cancer ($P < 0.05$). Targeting Kif18A for therapeutic intervention, it may also have utility as a tumor biomarker for gastric cancer prognosis.

P303

Warfarin Blocks Gas6-mediated Axl Activation Required for Pancreatic Tumor EMT and Metastasis
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Warfarin, an anti-coagulant in clinical use for over 50 years, is reported to exert anti-cancer and anti-metastatic effects; however, a mechanism of action consistent with the anti-tumor activity has not been elucidated. Interaction of the vitamin K-dependent Gas6 ligand with the receptor tyrosine kinase, Axl, is potently inhibited by warfarin at doses lower than those required for anti-coagulation. Expression of Axl in pancreatic cancer is associated with increased metastasis and shorter survival. We hypothesized that the molecular mechanism underlying the anti-tumor effects of warfarin is due to inhibition of Gas6 activation of Axl. In vivo therapy with low dose warfarin resulted in dramatically reduced cancer progression in three orthotopic pancreatic cancer models as well as a genetic model of pancreatic cancer (p48-Cre; KrasG12D;Cdkn2alox/lox). Furthermore, warfarin inhibited Axl signaling as measured by activation of Erk and Akt in tumor lysates. Warfarin therapy demonstrated increased efficacy when administered prior to tumor cell injection as well as enhanced response to chemotherapy with gemcitabine. Comparatively, warfarin did not affect the growth of Capan-1, an Axl negative cell line. However, direct targeting of Axl with a neutralizing monoclonal anti-Axl antibody or stable knockdown in Mia PaCa2 cells, resulted in suppression of tumor growth documenting the functional importance of Axl to pancreatic tumor progression. In vitro warfarin treatment inhibited Axl dependent invasion and migration, while increasing apoptosis and sensitizing cells to gemcitabine treatment. Congruently, warfarin blocked Axl-dependent maintenance of a mesenchymal phenotype induced by TGF-β and collagen. These findings are consistent with an increase in therapy-sensitive epithelial characteristics and apoptotic activity in tumors from animals treated with warfarin. These findings strongly support the clinical evaluation of subtherapeutic warfarin and other Axl-targeting agents as a novel therapeutic strategy in pancreatic cancer patients.

P304

Pancreatic Intraepithelial Neoplasia in Non-Adenocarcinoma Pancreatic Tumors. What is its Clinical Significance?
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Background: Pancreatic Intraepithelial Neoplasia (PanIN) is a presumed precursor of pancreatic ductal adenocarcinoma (PDAC). Reports have suggested that PanIN in non-PDAC lesions may indicate increased risk for developing PDAC. Aim: To assess the impact of incidental PanIN, after resection for non-adenocarcinoma lesions, on the development of metachronous PDAC in the remnant.Materials and Methods: Retrospective review of clinicopathologic data of patients who underwent pancreatectomy for non-adenocarcinoma from 1/2000-1/2010. Intraductal papillary mucinous lesions were excluded. All available postoperative radiological study reports were reviewed. Results: Inclusion criteria were met by 584pts. Median age was 59yrs(range:10-85yrs) and 338(58%) were female. Most common procedure was distal pancreatectomy(55%). The two most common lesions(55%) were serous cystic neoplasm and pancreatic neuroendocrine tumor (others: mucinous cystic neoplasms, solid pseudopapillary tumors, acinar cell neoplasms, sarcomas, chronic pancreatitis, metastases, ampullary adenomas, benign cysts, others). PanIN was identified in 153(26%)pts the majority of whom had PanIN1 or 2 (50% and 41%, respectively) whereas 13(9%) had PanIN3. Patients with PanIN3 had more advanced median age (70vs62vs58yrs;$p<0.001$) and co-existent pancreatitis (61%vs29%vs18%;$p=0.006$) compared to PanIN1-2 and PanIN0 respectively. Follow-up of more than 6mo was available in 506(87%)pts with imaging available in 424(73%). After a median follow-up of 3.7yrs no PanIN0 patient developed pancreatic cancer, while only 1(0.6%) patient with PanIN developed cancer in the remnant, which was diagnosed 4.4yrs after a distal pancreatectomy for a retention cyst in the setting of PanIN1B. Of note, none PanIN3 patient developed cancer on follow up.Conclusion: Pancreatic Intraepithelial Neoplasia was identified in 26% of non-adenocarcinoma patients. Higher grade lesions were more frequently found in older patients. The presence of PanIN of any grade did not predispose to cancer development in the pancreatic remnant, and routine follow-up imaging for this finding does not seem warranted.

P305

Patterns of Recurrence and Outcomes in Pancreatic Cancer
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INTRODUCTION: There is limited evidence supporting improved overall survival in patients with pancreatic cancer with isolated lung metastases compared to other metastatic sites. We reviewed our experience with patterns of metastases and outcomes in pancreatic cancer. METHODS: A retrospective review of 378 patients who underwent potentially curative pancreatic resection for pancreatic adenocarcinoma at a tertiary care cancer center between 1997-2010. All patients were restaged in accordance with AJCC 7th edition guidelines. Kaplan-Meier analysis with log-rank test and Cox regression was used to compare median overall and disease-free survival (OS and DFS). RESULTS: Patients were divided into 8 groups based upon site of first recurrence. 40% of patients were without evidence of recurrence at time of last follow up (n=165). Sites of first recurrence are as follow: liver (n=93, 24.6%), lung (n=37, 9.8%), locoregional (n=49, 13%), peritoneum (n=17, 4.5%), bone (n=6, 1.6%), and distant (n=2, 0.5%). 23 patients (6.1%) presented with multiple sites as first recurrence. Patients with isolated lung metastases had longest median OS while those with liver metastases had the shortest median OS (32 months vs. 17 months, $p<0.001$). Time to recurrence for lung vs. liver metastases was 14.9 vs. 7.4 months ($p<0.005$). Patients with liver metastases uniformly had significantly worse median OS as compared to other sites of recurrence. Finally, with respect to isolated lung recurrences, only CA19-9 was a significant prognostic factor. Those patients with a CA19-9 at diagnosis >185 had a 5-fold greater risk of death in our length of follow-up. CONCLUSIONS: Pancreatic cancer patients with isolated lung metastases as the site of first recurrence have improved OS compared to other sites, while patients with liver metastases have worse OS. CA19-9 >185 at time of diagnosis among patients with isolated lung recurrences was predictive for worse outcomes.

P306

D2 Lymphadenectomy and *Ex Vivo* Dissection into Node Stations for Gastric Adenocarcinoma Ensures Optimal Staging
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Introduction: The AJCC recommends >16 nodes be examined to adequately stage gastric adenocarcinoma. D2 lymphadenectomy (LAD) followed by ex vivo dissection (EVD) of the surgical specimen into nodal stations is standard

at many high-volume Asian centers and may improve staging and overall survival (OS). Methods: 331 patients with resectable gastric adenocarcinoma underwent potentially curative surgical resection from 1995-2010. Extent of surgery, LAD, and EVD were examined. Cox proportional hazards methods was used to assess factors related to OS. Results: Median age of patients was 69 years old, 65% were male, 84% were Caucasian, and 86% were symptomatic (most frequently GI bleeding/anemia, abdominal pain/discomfort, and anorexia/weight loss). Tumors were distributed equally throughout the stomach, and 47% were poorly differentiated. Extent of gastric resection was distal/subtotal in 43%, proximal or esophagogastrectomy in 29%, and total in 28%. D1 LAD was performed in 285 patients (86%) and D2 LAD in 46 patients (14%), with EVD being performed in 17 patients (37%) in the D2 group. For the D1, D2 without EVD, and D2 with EVD groups, median number of examined nodes (interquartile range) and percent >16 examined nodes was 16 (10-21) and 51%, 30 (20-34) and 93%, and 40 (28-59) and 100%. Median length of stay and 30-day mortality were 9 days and 2.5% for the D1 group and 8 days and 0% for the D2 group, respectively. Despite the D1 and D2 groups having similar stages of disease, the D2 group had better OS compared to the D1 group for all patients as well as for the subgroup of patients with positive nodes. (fig.1) On both univariate and multivariate analysis of OS, D2 LAD was a positive prognostic factor (p=0.027 and 0.005). Conclusions: D2 LAD at our institution was performed with low morbidity and mortality and increased the proportion of patients having the recommended >16 examined nodes from 51% to 93%. Other potential benefits of D2 LAD may include improved overall survival, but this requires further prospective trials. D2 LAD and EVD resulted in optimal node staging, with 100% of patients having >16 examined nodes.

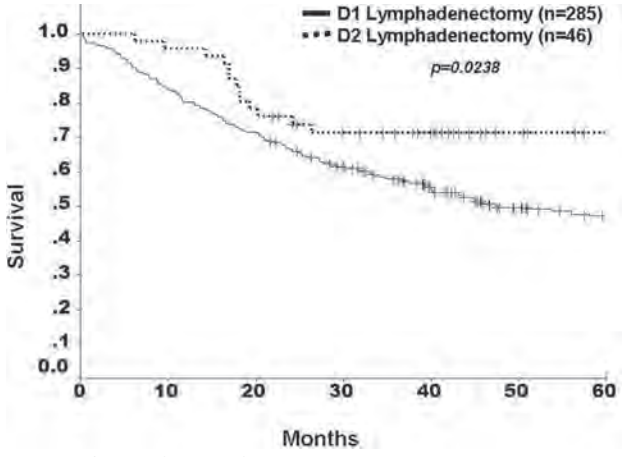

Figure 1: Overall Survival Stratified by Extent of Lymphadenectomy

P307

Pathologic Stage after Neoadjuvant Therapy for Esophageal Cancer is More Predictive of Survival than Initial Clinical Stage

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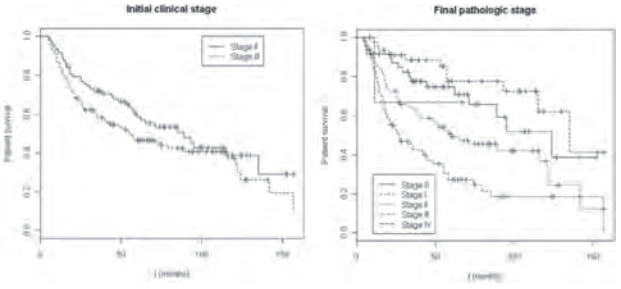
Introduction. In patients with locoregionally advanced esophageal carcinoma, neoadjuvant therapy can improve survival. The question remains as to whether survival is better predicted by the initial clinical or the final pathologic stage. Methods. Retrospective review was performed for all patients who underwent resection after neoadjuvant therapy for stage II-III esophageal cancer at a tertiary care referral center from January 2000 to June 2012. The impact of various clinicopathologic factors on overall survival was assessed with univariate and multivariate analyses. Results. A total of 293 patients with a median age of 63 were treated with neoadjuvant chemotherapy (n=230) or chemoradiotherapy (n=63) followed by resection. Most patients were male (80.2%), had adenocarcinoma (80.2%), had a tumor in the distal esophagus (85.6%), had a moderately differentiated tumor (49.1%), and had transhiatal esophagectomy (87.0%) with r0 resection (93.2%). Mortality was 4.4%, with complications in 46.1% patients. Downstaging occurred in 51.9% of patients. Overall survival was predicted by final pathologic stage ($p<0.001$), but not initial clinical stage ($p=0.087$)(See Figure 1). Median survival based on initial stage was 89 and 56 months for stages II and III. Median survival based on final pathologic stage was 124, 135, 60, and 27 months for stages 0-III. When compared to historical survival rates, patients that were downstaged to stage 0 or I had better survival than initial stage II or III disease would predict, but worse than what would be expected for stage 0 or I. Patients with stage II or III disease on final pathology had survival rates comparable to what is expected for stage II or III disease. Multivariate analysis demonstrated age ($p<0.001$) and response to neoadjuvant therapy ($p<0.001$) to be factors predictive of overall survival. Conclusion. In patients with esophageal cancer that undergo neoadjuvant therapy, survival is better predicted by final pathologic stage than by initial clinical stage. Age and response to neoadjuvant therapy are significant predictors of overall survival.



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Differential HER2 Expression in Resected Gastric Cancer: Is There Prognostic Value?

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Introduction: For advanced gastric cancer, the ToGA trial established HER2 as an important therapeutic target in the 20% of patients whose tumors exhibited HER2 overexpression or gene amplification. Others have reported that HER2-positive tumors are associated with poor survival in advanced disease. The expression profile and prognostic value of HER2 in resectable gastric cancer are unknown. Methods: 111 pts underwent curative intent resection of gastric adenocarcinoma between 1/00-6/11 and had tissue available for analysis. Immunohistochemistry (IHC) for HER2 was performed on banked tumor specimens and graded by two pathologists blinded to outcomes utilizing ToGA trial criteria. An IHC score of 0+ or 1+ was regarded as negative, 3+ as positive. Fluorescence in-situ hybridization (FISH) for HER2 was performed on equivocal (2+) IHC samples. Primary outcome was differential expression, secondary outcome was overall survival (OS). Results: Median age was 64yrs, 54% were male. Median tumor size was 4cm, 7.2% had a positive margin, 67.6% were poorly differentiated, 23.4% had perineural invasion, 35.1% had lymphovascular invasion, and 61.3% had nodal metastases. 24 patients had stage I disease (21.6%), 32 stage II (28.8%), and 55 stage III (49.6%). Mean follow-up was 28.9mos, median OS was 27.2mos. HER2 expression by IHC was negative in 61 (55%), equivocal in 37 (33.3%), and positive in 13 (11.7%). Of the 37 equivocal cases, FISH was positive in 8, for a total of 21 HER2-positive cases (18.9%) and 90 HER2-negative cases (81.1%). HER2 status did not correlate with T or N stage, tumor size or location, tumor grade, or perineural or lymphovascular invasion. HER2 status was not associated with OS ($p=0.36$). Conclusions: Resectable gastric cancer exhibits differential expression of HER2, similar to that of advanced disease. Despite reports suggesting HER2 positive status is associated with aggressive disease and worse outcomes in the advanced setting, HER2 status is not associated with adverse pathologic factors or survival in resectable disease. Although not prognostic, the predictive value of HER2 status for response to trastuzumab in the adjuvant setting requires further investigation.

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Trametinib in Combination with Panitumumab and Trastuzumab Inhibits Tumor Growth in an Orthotopic Xenograft Model of Human Pancreatic Cancer J.M. Lindberg,* S.J. Adair, T.E. Newhook, A. Kim, J. Parsons, T.W. Bauer. *Surgery, University of Virginia, Charlottesville, VA.*

Introduction: Aberrant *Kras* and EGFR family signaling are key drivers of pancreatic ductal adenocarcinoma(PDAC). We hypothesized that combination trametinib(MEK1/2 inhibitor), panitumumab(EGFR inhibitor) and trastuzumab(Her2 inhibitor) would more effectively suppress tumor growth than any of these monotherapies. *Methods:* Patient-derived PDAC cell line MAD09-366 was exposed to trametinib, panitumumab, trastuzumab, and combination therapies *in vitro*. Western blot analysis was performed on treated cell lysates. Athymic, nude mice were orthotopically implanted with 3 different patient-derived PDAC xenografts(MAD09-366, 08-608, and 08-738). Established murine tumors were treated with control, trametinib(0.3mg/kg, qDay), panitumumab(500ug, BIW), trastuzumab (200ug, BIW) or in combination. MRI was used to assess tumor response. *Results:* Two of 3 PDACs were *Kras* mutant, 2 of 3 demonstrated increased Her2 activity, and all 3 showed increased EGFR activity. *In vitro* studies demonstrated improved growth inhibition of MAD09-366 cells exposed to triple therapy relative to control or each inhibitor alone. Western blot analysis revealed that EGF stimulation increased Ras pathway signaling in this *Kras* mutant cell line. With EGF stimulation, the greatest Ras pathway signaling inhibition was seen in triple-therapy-treated cells. *In vivo* studies in all PDAC xenografts revealed that triple therapy significantly decreased tumor growth rate relative to control, trametinib alone, panitumumab alone, or panitumumab plus trastuzumab. In 2 of 3 PDACs assessed, triple therapy was superior to trametinib plus panitumumab. The greatest response was seen in MAD08-738 triple-therapy-treated mice whose average tumor size decreased by 9.3%. *Conclusions:* Combination therapy with trametinib, panitumumab, and trastuzumab demonstrated the greatest *in vitro* Ras signaling blockade. This combination was well tolerated *in vivo* and generated significant tumor growth inhibition or regression in all patient-derived tumors assessed. This treatment strategy should be considered for a future clinical trial in pancreatic cancer patients.

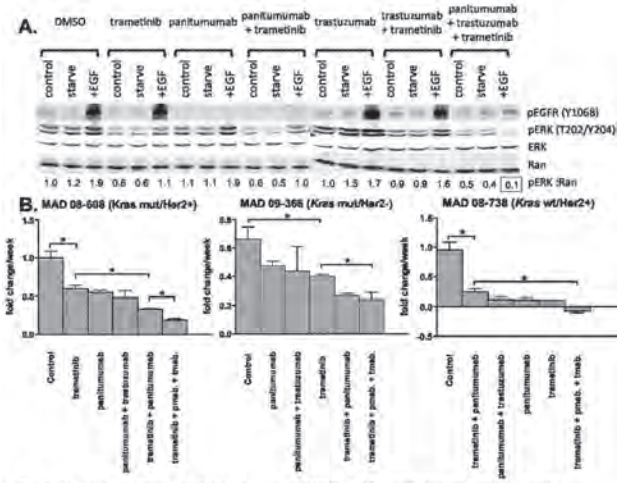

Fig. 1 – A. *In vitro* effects of inhibitor therapy on EGFR and Ras-pathway signaling in patient-derived MAD09-366 cells. Cells in each treatment group were either starved, EGF stimulated, or controls prior to lysis. **B.** *in vivo* response to drug therapy of tumor bearing mice under each treatment condition. Each treatment group contained 4-5 mouse replicates. Presented is the mean fold change in tumor volume per week of treatment. *p < 0.05 vs. comparison group.

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Interleukin-1 as a Mediator of Angiogenesis in Pancreatic Adenocarcinoma K. Turner,[1]* S. Houng,[1] S. Varghese,[2] H.R. Alexander.[2] *1. Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; 2. Department of Surgery, Division of Surgical Oncology and The Greenbaum Cancer Center, University of Maryland Medical Center, Baltimore, MD.*

INTRODUCTION: IL-1 is a pluripotent cytokine that mediates progression of cancers via proliferative and angiogenic mechanisms. We have previously shown that the functional IL-1 receptor (IL-1R) is expressed in Panc Ca cell lines and that constitutive IL-1 gene expression varies. We hypothesized that inhibition of IL-1 signaling suppresses pancreatic adenocarcinoma (Panc Ca) growth and angiogenesis. METHODS: Three Panc Ca cell lines previously characterized as expressing the IL-1R and either high (H; Panc 02.03 & Panc 03.27 with >10^3 copies of IL-1 gene/10^5 β-actin) or low (L; Mia PaCa-2) IL-1β gene expression were chosen for study. IL-1β was measured (ELISA) in cell culture lysates and in vivo from wild type Panc Ca tumor xenografts. Cell proliferation (WST-1), VEGF, and IL-8 (ELISA) were measured in all cell lines after exposure to IL-1β, IL-1Ra, and IL-1β antibody. Growth of tumor xenografts of Panc 02.03 (H) retrovirally transfected to overexpress IL-1Ra was determined. RESULTS: IL-1β was detected in cell lysates from cell culture and tumor xenografts; however, secreted IL-1β was not detected in cell culture supernatants. Proliferation was unaffected in all cell lines by IL-1β, IL-1Ra, or IL-1β antibody. However, dose dependent IL-8 production was observed in all cell lines after IL-1β and this effect was attenuated by IL-1Ra and IL-1β antibody. VEGF production was unaffected. In vivo, there was marked growth inhibition of Panc 02.03 (H) IL-1Ra transfected xenografts compared to null transfectants ($p<.05$). CONCLUSION: The IL-1 signaling pathway is intact in pancreatic adenocarcinoma. IL-1 signaling does not appear to mediate cell proliferation but markedly affects production of the angiogenic factor IL-8 in vitro. As suggested by in vivo data, inhibition of the IL-1 pathway in tumor xenografts leads to decreased tumor growth. As such, IL-1 signaling promotes an angiogenic phenotype in Panc Ca and IL-1 inhibition may be a promising target for further study in this cancer.

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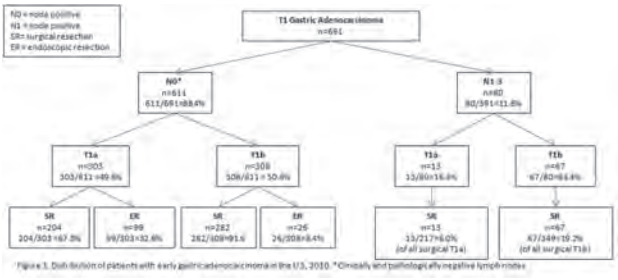
Current Utilization of Endoscopic Resection and Risk of Lymph Node Metastases for Early Gastric Cancer in the U.S. K.L. Sherman,[1]* R.P. Merkow,[2] R.N. Keswani,[3] K.Y. Bilimoria,[1] D.J. Bentrem.[4] *1. Department of Surgery and Surgical Outcomes and Quality Improvement Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; 2. Department of Surgery, University of Colorado Denver Anschutz Medical Campus, Aurora, CO; 3. Department of Gastroenterology, Feinberg School of Medicine, Northwestern University, Chicago, IL; 4. Department of Surgery and Surgical Outcomes and Quality Improvement Center, Feinberg School of Medicine, Northwestern University and Department of Surgery, Jesse Brown VA Medical Center, Chicago, IL.*

Introduction: National guidelines advocate the use of endoscopic resection (ER) for early gastric cancer (EGC). The rate at which ER is being adopted for EGC is unknown. A few series have begun to define the risk of lymph node involvement for T1 lesions but U.S. data is scarce. Our objectives were to (1) evaluate current practice patterns in T1a/T1bN0 gastric cancer, (2) identify predictors of ER for T1a disease and (3) compare lymph node metastasis rates among surgical T1a and T1b patients. Methods: The National Cancer Data Base was used to retrospectively analyze patients with T1 gastric adenocarcinoma who underwent endoscopic or surgical resection in 2010. Models predicted ER among patients with T1aN0 disease. All surgical T1a/b patients were evaluated to determine the unexpected and overall nodal metastatic rates. Results: We identified 691 patients with T1a (n=316, 45.7%) or T1b (n=375, 54.3%) gastric cancer (Figure 1). Of patients with T1aN0 disease, 67.3% (n=204) were treated with surgical resection and 32.6% (n=99) were treated with ER. Patients with T1bN0 disease were treated primarily surgically (91.6%, n=282). Among patients with T1aN0 gastric cancer (n=303), patients who were over 75 years (vs. <65 years: OR 8.08; CI 2.95-22.17) and patients with proximal lesions (vs. distal lesions: OR 8.41; CI 3.27-21.60) were more likely to undergo ER. No Asian patients underwent ER (n=22). We then examined surgical patients with T1a (n=217) or T1b (n=349) gastric adenocarcinoma. The unexpected nodal metastasis rate for T1a disease was 6.0% (n=13) compared to 19.2% (n=67) for T1b lesions ($p<0.001$). Including patients with clinically positive nodes (n=25), the overall nodal metastasis rates was 7.1% (n=16) for T1a lesions compared to 21.8% for T1b lesions (n=80, $p<0.001$). Conclusions: The majority of patients with EGC are treated by surgery. Older patients and those with proximal lesions are most likely to undergo ER. A small, but definable, risk of lymph node metastasis likely exists for patients undergoing endoscopic resection.



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Intraoperative Fluid Administration Rate Correlates with Perioperative Outcomes in Patients Undergoing Pancreaticoduodenectomy

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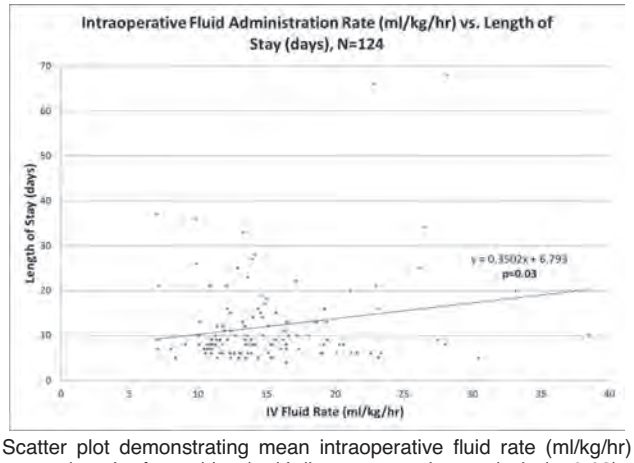
Introduction: Recent studies on the relationship between intraoperative fluid (IOF) administration and perioperative outcomes in patients undergoing pancreaticoduodenectomy (PD) have yielded conflicting results. An optimal intraoperative fluid administration rate has yet to be defined. Our aim was to further investigate this relationship. Methods: 124 patients who underwent PD from September 2007 to May 2012 at a single tertiary university center were identified from a retrospective database. Total IOF for each patient was calculated including crystalloid, colloid, blood products, and converted to a rate of ml/kg/hr. Patients were stratified into three IOF rate groups: <12, 12-16, and >16 ml/kg/hr. In another analysis, patients were divided into two groups by preoperative albumin, those ≤3.0 and >3.0 g/dL, with each subdivided by median IOF rate. Perioperative outcomes were compared, including length of stay and severity of complications (by Clavien-Dindo grade). Results: Mean age and underlying comorbidities among the <12 (N=36), 12-16 (N=49), and >16 (N=39) ml/kg/hr groups were similar, with the exception of preoperative albumins, which were 3.6, 3.5, and 3.2 g/dL respectively (p=0.01). With increasing IOF rate, mean estimated blood loss was 631ml, 675ml, and 1460ml (p<0.01). Mean Clavien-Dindo complication grades were 1.6, 1.3, and 2.6 (p<0.01). Mean lengths of stay were 10.9, 11.6, and 13.9 days respectively, and a linear regression analysis yielded a significant correlation between IOF rate and length of stay (p=0.03). In patients with a preoperative albumin of ≤3.0 (N=27), those who received greater than the median IOF rate experienced more severe complications (1.8 vs. 3.5, p=0.02). This difference was not significant in the >3.0 g/dL (N=97) group (1.4 vs. 1.7, p=0.31). Conclusion: Increased intraoperative fluid administration rate correlates with an increased length of stay. Severity of complications is increased in patients receiving >16 ml/kg/hr, suggesting an optimal fluid rate <16 ml/kg/hr. Patients with lower preoperative albumin and increased IOF rate are particularly associated with more severe complications.



Scatter plot demonstrating mean intraoperative fluid rate (ml/kg/hr) versus length of stay (days) with linear regression analysis (p=0.03)

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Trends in the Surgical Treatment of Gastric Adenocarcinoma

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Introduction: Over the past decade, the treatment of gastric adenocarcinoma has evolved due to the publication of two seminal randomized controlled trials. The National Cancer Data Base (NCDB) is a national oncology outcomes database for over 1,500 Commission on Cancer-accredited cancer programs. Our hypothesis was that the use of chemotherapy and chemoradiation in addition to surgery for treatment of gastric adenocarcinoma has increased from 2000-2009. Methods: Patients diagnosed with stage 1-3 gastric adenocarcinoma between 2000-2009 were selected from the NCDB Hospital Comparison Benchmark Reports. Attention was paid to the initial treatment regimen, such as surgery alone, surgery plus chemotherapy, or surgery plus chemoradiation. In addition, data on hospital setting was collected and analyzed. The Cochran-Armitage test for trend was used to assess changes in treatment over time. Results: 48, 727 patients with stage 1-3 gastric adenocarcinoma were included in the analysis. Between 2000-2009, the use of surgery alone for first course treatment across all three stages decreased significantly at both teaching-research hospitals and community hospitals (p<0.0001 for all cases). In the same period, the use of chemotherapy in addition to surgery as treatment increased significantly across all three stages and at both types of hospitals (p<0.001 for all cases). Treatment with surgery plus chemoradiation increased for stage 1 and 2 diseases at community hospitals (p=0.0073 and 0.0014, respectively), but did not change significantly for stage 3 disease (p=0.41). There was no significant change at teaching-research hospitals in the use of surgery plus chemoradiation (p>0.4 for all cases). Non-surgical treatment increased across all stages at both types of hospitals (p<0.05 for all cases). Conclusions: Data from the NCDB from 2000-2009 demonstrates that the trend for the surgical treatment of gastric adenocarcinoma shows the increasing use of multimodality therapy as opposed to surgery as sole therapy.

		Surgery Only		Surgery plus Chemotherapy		Surgery plus Chemoradiation		No Surgical Therapy	
		Cochran-Armitage Test for Trend p value	Percent Change between 2000 and 2009	Cochran-Armitage Test for Trend p value	Percent Change between 2000 and 2009	Cochran-Armitage Test for Trend p value	Percent Change between 2000 and 2009	Cochran-Armitage Test for Trend p value	Percent Change between 2000 and 2009
Stage 1	Teaching-Research Hospitals	<.0001	-11.53%	<.0001	198.13%	0.6856	3.24%	0.002	15.05%
	Community Hospitals	<.0001	-25.57%	<.0001	68.34%	0.0073	18.63%	<.0001	70.51%
Stage 2	Teaching-Research Hospitals	<.0001	-48.39%	<.0001	146.15%	0.4762	9.40%	<.0001	94.25%
	Community Hospitals	<.0001	-39.14%	0.0001	29.07%	0.0014	16.89%	<.0001	101.14%
Stage 3	Teaching-Research Hospitals	<.0001	-47.84%	<.0001	99.17%	0.6469	-6.84%	<.0001	61.87%
	Community Hospitals	<.0001	-35.45%	0.0009	34.38%	0.4088	0.31%	<.0001	69.06%

No Surgical Therapy includes no first course therapy, chemotherapy only and chemoradiation only.

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Superior Antitumor Activity of Nanoparticle Albumin-Bound Paclitaxel in Experimental Gastric Cancer

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Background: Gastric cancer is the second most common cause of cancer related death worldwide and lacks highly effective adjuvant or definitive systemic treatment for advanced disease. Nab-paclitaxel is a novel microtubule-targeting cytotoxic agent and not tested in gastric cancer as of yet. Methods: Human gastric cancer cell lines AGS, NCI-N87 and SNU16 were studied for treatment effects on cell proliferation, mitotic arrests and apoptosis in vitro and vivo. Tumor growth and survival studies were performed in murine xenografts. Results: Nab-paclitaxel inhibited cell proliferation with an IC50 of 2.01 nM in SNU16, 23.3 nM in AGS and 48.69 nM in NCI-N87 cells after 72-hour treatment, which was lower than that of oxaliplatin (1.05μ M to 1.51μM) and epirubicin (0.12 μM to 0.25 μM). Nab-paclitaxel treatment caused increased expression of the mitotic-spindle associated phospho-stathmin, nuclear fragmentation or karyopyknosis, and apoptotic events as confirmed through increased expression of cleaved-PARP and caspase-3. After a two-week nab-paclitaxel, oxaliplatin or epirubicin treatment, the local tumor growth inhibition rate was 77, 17.2 and 21.4 percent, respectively (p=0.002). Effects of therapy on tumoral

proliferative and apoptotic indices corresponded with tumor growth inhibition data, while expression of phospho-stathmin also increased in tissues. There was an increase in median animal survival after nab-paclitaxel treatment (86 days) compared to controls (24 days, p=0.0004) or to oxaliplatin therapy (37.5 days, p=0.0005). Conclusions: The strong antitumor activity of nab-paclitaxel in experimental gastric cancer supports such microtubule-targeting therapy for clinical application. Nab-paclitaxel benefits were observed independent from phosphorylated stathmin expression at baseline, putting into question the consideration of nab-paclitaxel use in gastric cancer based on this putative biomarker.

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Pancreaticoduodenectomy – Multivisceral Resection Adds Morbidity: A NSQIP Analysis N. Bhayani,* E.T. Kimchi, J. Kaifi, K.F. Staveley-O'Carroll, N.J. Gusani. *Penn State Hershey Medical Center, Hershey, PA.*

INTRODUCTION Pancreaticoduodenectomy (PD) for peri-ampullary lesions is a complex procedure which can be performed with low mortality but significant morbidity. En-Bloc multivisceral resection (MVR) may be undertaken at PD (PD+MVR) to achieve complete extirpation. Aside from single-institution studies, the morbidity of PD+MVR is not well defined. METHODS We examined all 8522 PD cases from the 2005-2010 National Surgical Quality Improvement Project (NSQIP) database. Stepwise logistic regression was employed to determine 1) if MVR independently predicts morbidity & mortality and 2) if a particular organ resection was associated with increased morbidity. RESULTS MVR was performed in 296 patients (3.5% of PD cases). Preoperative co-morbidities were similar for those having PD vs PD+MVR. Fewer patients having PD+MVR had periampullary malignancy or benign disease (p<0.001), compared to PD alone. MVR included liver (46%), colon (44%), small bowel (23%), and stomach (10%) resection procedures. Mortality (8.5% vs 2.8%) & morbidity (61% vs 38%) were higher for PD+MVR vs PD alone (p<0.001). This was due to higher rates of organ-space infection, pulmonary complications, renal failure, cardiac arrest, bleeding, sepsis, and septic shock. (Table 1) On multivariable regression MVR was an independent predictor of death (OR 2.9, p<0.001), overall morbidity (OR 2.6, p<0.001), major morbidity (OR 2.7, p<0.001), and minor morbidity (OR 1.36, p=0.04). Among patients having PD+MVR, colectomy was an independent predictor of increased overall morbidity (OR 3.4, p<0.001) and major morbidity (OR 3.0, p<0.001). CONCLUSIONS Multivisceral resections at the time of pancreatoduodenectomy may be performed to obtain R0 resection. These complex resections nearly triple mortality & add substantial morbidity to PD. MVR is an independent predictor of death and morbidity during PD. Colectomy was among the most common additional organs resections performed, but tripled the likelihood of major morbidity. MVR at PD increases morbidity and should be approached with caution.

Table 2. Outcomes

	Pancreato-Duodenectomy	Multi-Visceral Resection	
	n=8226 (96%)	n=296 (4)	p-value
Death	233 (2.8)	25 (8.4)	<0.001
Any Morbidity	3124 (38)	180 (61)	<0.001
Major Morbidity	2369 (29)	153 (52)	<0.001
Minor Morbidity	1381 (17)	65 (22)	0.02
Organ-Space Infection	851 (10)	59 (20)	<0.001
Pneumonia	427 (5.2)	29 (9.8)	0.001
Reintubation	420 (5.1)	30 (10)	<0.001
Prolonged Intubation	449 (5.5)	38 (13)	<0.001
Thromboembolism	235 (2.9)	15 (5.1)	0.03
Cardiac Arrest	102 (1.2)	11 (3.7)	<0.001
Bleeding	546 (6.6)	42 (14)	<0.001
Sepsis	888 (11)	61 (21)	<0.001
Shock	360 (4.4)	30 (10)	<0.001
Renal Failure	95 (1.2)	8 (2.7)	0.02

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Effect of Body Mass Index in Patients Undergoing Resection for Gastric Cancer: A Single Center U.S. Experience J. Wong,* S. Rah-man, N. Saeed, H. Lin, K. Almhanna, R. Shridhar, S. Hoffe, K. Mered-ith. *Surgery, Moffitt Cancer Center, Tampa, FL.*

Introduction: With the rise of obesity in the U.S., the impact of body mass index (BMI) on surgical outcomes and survival in gastric cancer remains undetermined. Methods: An IRB-approved, prospectively-maintained institutional database of patients referred for surgical evaluation of gastric cancer was reviewed. Patients were stratified according to BMI: <18.5 (underweight), 18.5-25 (normal weight), 25.1-30 (overweight), and >30 (obese). Clinicopathologic factors and overall survival (OS) were analyzed using polytomous regression, Pearsons correlation and Kaplan Meier when appropriate. Results: From 1997-2012, 222 patients underwent exploration for gastric adenocarcinoma. Of these, 186 (84%) patients had BMI recorded: 9 (5%) with BMI<18.5, 72 (39%) 18.5-25, 62 (33%) 25.1-30, and 43 (23%) >30. 135 (73%) ultimately underwent resection. Operative factors including American Society of Anesthesiology (ASA) score and blood loss were not significantly associated with BMI. Increased BMI was associated with longer operative time, P=0.02. Pathologic factors including proximal tumor location, perineural invasion (PNI), lymphovascular invasion (LVI), positive surgical margins, and positive lymph nodes (LN+) were all associated with a worse OS. Although increased BMI was associated with a lower total lymph node count, P=0.004, the number of LN+ was not associated with BMI. Tumor location, PNI, LVI, margin status, and final pathologic stage were not significantly associated with BMI. Additionally, the use of neoadjuvant or adjuvant chemotherapy was not associated with BMI. Median OS for the group was 22 months. When stratified by BMI, median OS was improved with increased BMI: 21 months for <18.5, 13 months for 18.5-25, 28 months for 25-30, and 34 months for >30, P=0.02. Similarly, disease free survival (DFS) improved with increasing BMI: 2 months for <18.5, 7 months for 18.5-25, 15 months for 25.1-30, and 15 months for >30, P=0.02. Conclusion: Although BMI may impact the technical difficulty of resection for gastric cancer, increasing BMI is not associated with more aggressive disease. In this experience, increased BMI does not adversely impact OS or DFS.

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Impact of Neoadjuvant Chemoradiotherapy on Postoperative Course after Curative Intended Transthoracic Esophagectomy in Esophageal Cancer Patients D. Bosch,* C.T. Muijs, G.A. Hospers, V.E. Mul, J.T. Plukker. *University Medical Centre Groningen, Groningen, Netherlands.*

Background: Neoadjuvant chemoradiotherapy (CRT) improves loco-regional control and overall survival in esophageal cancer patients. Although relatively low adverse effects are encountered during CRT, severe postoperative side-effects may occur leading to increased morbidity and even mortality. Therefore, we investigated the impact of a currently used preoperative CRT regimen of 41.4Gy/5wks with concurrent Carboplatin and Paclitaxel (CROSS scheme) on the postoperative course. Patients and methods: Between 2006 and 2012, a total of 96 patients were treated neoadjuvantly according to the above scheme. These patients were matched with 96 patients who underwent surgery alone, from a prospectively maintained database on: gender, age, comorbidity (diabetes mellitus, hypertension, angina pectoris, heart failure, myocardial infarction, COPD, TIA/CVA), ASA classification and side of thoracotomy. Results: Surgical mortality (90-day and/or in-hospital mortality) and 30-day mortality did not differ between both groups. In the neoadjuvantly treated group significant more patients were diagnosed with pneumonia (27,1% vs 51,0%; p=0.001), pleural effusion (13,5% vs 25,0%; p=0.044) and arrhythmias (20,4% vs 34,4%; p=0.008). Besides, in the multivariate analyses neoadjuvant CRT was significantly associated with an increased risk of pneumonia (p=0.000 odds ratio 3,267) and arrhythmia (p=0.012 odds ratio 2,617). Despite these outcomes, no differences were detected in ICU - and in hospital stay. Conclusions: In this study, the observed increase of postoperative respiratory events and arrhythmia in the neoadjuvant CRT group has no effect on hospital or ICU stay and mortality. However, further research is warranted on limitation of radiation-induced lung –and cardiac toxicity.

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Clinicopathological and Prognostic Significance of Fibroblast Growth Factor Receptor 1, 2, and 4 in Gastric Cancer H. Murase,[1]* M. Inokuchi,[1] H. Sugita,[1] K. Kato,[1] K. Kojima,[2] K. Sugihara.[1]
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Introduction: The overexpression of fibroblast growth factor receptor (FGFR) 2 has been known as a prognostic factor and a target of treatment in gastric cancer. However, role of the other FGFRs is not elucidated enough. We investigated the correlations of FGFR1-4 expressions with clinicopathological features and prognosis in gastric cancer. Materials & Methods: Tumor samples were obtained from gastric adenocarcinomas of 223 patients who

underwent a gastrectomy from 2003 to 2007. The expression of each FGFR was analyzed in the tumor by immunohistochemistry. Parametric correlations were done between FGFR expressions and the clinicopathologic findings. A univariete and multivariate analysis were done with the disease specific survival. Results: Cytoplasmic overexpression of FGFR1 was found in 64 (29%) of all tumors, FGFR2 in 115 (52%), FGFR3 in 143 (64%), and FGFR4 in 175 (78%). A significant relationship was observed between the expression of FGFR1 and FGFR2, FGFR1 and FGFR4, and FGFR2 and FGFR4 (P<0.0001, <0.0001, and <0.0001, respectively).Overexpression of FGFR1, 2 or 4 was significantly associated with tumor progression, including the depth of tumor invasion, involved lymph nodes, distant metastasis, tumor stage and recurrent disease. Patients with overexpression of FGFR1, 2 or 4 had significantly worse survival(p<0.0001, =0.0066, and 0.0003). In addition, co-overexpression of the three FGFRs was significantly associated with a poor survival than none or one expression of those expressions(p<0.0001 and =0.0006). Although the tumor stage was the most dominant prognostic factor (hazard ratio, 23.949; 95% confidence interval, 10.771-53.251; P<0.0001), The co-overexpression of the three FGFRs was also an independent prognostic factor (hazard ratio, 1.768; 95% confidence interval, 1.064-2.936; P = 0.028). Conclusions: Overexpression of FGFR1, 2, or 4 was associated with tumor progression and poor survival.FGFR1 and 4 may become prognostic factors and targets of treatment as well as FGFR2.

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Neoadjuvant Chemoradiation in Patients Undergoing Pancreaticoduodenectomy: Do the Ends Justify the Means? J.M. Hanna,* K. Penne, K. Rialon, M. Bashir, D.G. Blazer, III, B. Clary, R. White, T. Pappas, D.S. Tyler. *Department of General Surgery, Duke University Medical Center, Durham, NC.*

Purpose: The use of neoadjuvant chemoradiation in patients with resectable pancreatic cancer incorporates interventions that may significantly increase perioperative morbidity. The aim of this study was to review our single-institution experience with patients undergoing pancreaticoduodenectomy over a 15-year period and determine the morbidity and mortality associated with neoadjuvant therapy. Methods: This was a retrospective study of 563 patients undergoing pancreaticoduodenectomy from February 1995 to December 2011. Results: The neoadjuvant therapy cohort notably had a significantly higher rate of pre-operative biliary stenting and stent exchange than the pancreaticoduodenectomy first cohort. Multivariate regression analysis identified neoadjuvant therapy as an independent predictor of decreased pancreatic leak (p<0.0001), but increased rates of bacteremia (p=0.01) and wound (p=0.0002) and Clostridium difficile infection (p<0.0001). Additionally, 30-day mortality was significantly higher in this cohort (p=0.01), with most cases attributable to septic complications. A subset analysis of 244 pancreatic adenocarcinoma patients were compared on the same characteristics. Although there was a significantly decreased rate of pancreatic leak (p<0.0001), again there was an increased rate of wound (p=0.03) and Clostridium difficile infection (p=0.05) as well as 30-day mortality (p=0.05), with 9/16 (56%) being attributable to septic complications. However, neoadjuvant therapy was only identified as an independent predictor of decreased pancreatic leak (p=0.001). Additionally, overall long-term survival was improved in the neoadjuvantly treated cohort (p=0.01). (Table 1) Conclusion: In this single-center series comparing pancreaticoduodenectomy first versus neoadjuvantly treated patients, neoadjuvant chemoradiation confers a protective effect on pancreatic leak rate, but at a significant cost of increased peri-operative morbidity and mortality related to infectious complications. However, given the improved long-term survival, further studies are warranted to better understand how to minimize the morbidity attributable to neoadjuvant therapy.

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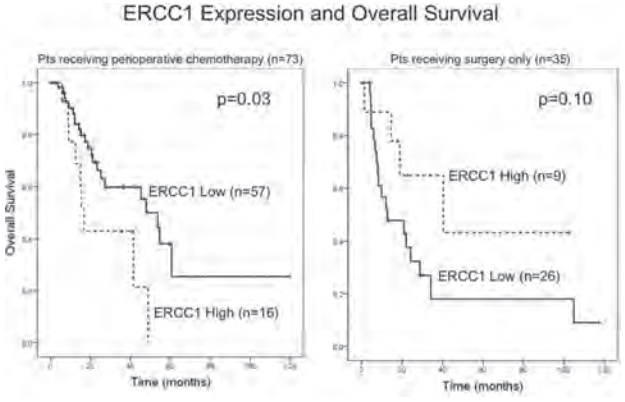
Differential Expression and Prognostic Value of ERCC1 and Thymidylate Synthase in Resected Gastric Adenocarcinoma M.H. Squires,[1]* S.B. Fisher,[1] K.E. Fisher,[2] S.H. Patel,[1] D. Kooby,[1] C.A. Staley,[1] A.B. Farris,[2] S.K. Maithel.[1] *1. Division of Surgical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; 2. Department of Pathology, Emory University, Atlanta, GA.*

Introduction: Excision repair cross complementing gene-1 (ERCC1) and thymidylate synthase (TS) are key regulatory enzymes whose expression patterns are variably associated with overall survival (OS) in several malignancies. For example, in lung cancer, high ERCC1 expression is inversely associated with OS depending on whether or not patients receive perioperative chemotherapy with surgery. The expression pattern and prognostic value of ERCC1 and TS in resected gastric adenocarcinoma (GAC) are not known. Methods: 109 patients who underwent resection of GAC between 1/00-6/11 had tissue available for analysis. Primary objective was to assess for differential expression of ERCC1 and TS using immunohistochemistry. Secondary objective was to assess for association of ERCC1 and TS expression with OS. Results: Median age was 64yrs. Median FU was 21.2mos and median OS was 28.8mos. Resected GAC exhibited differential expression of ERCC1 (23% high, n=25) and TS (43% high, n=47). ERCC1 and TS expression were not associated with OS. In a planned subset analysis, however, of patients who received chemotherapy (n=73), high ERCC1 expression was associated with decreased OS (16.7 vs 53.8mos; p=0.03; Figure). After controlling for tumor size, margin, grade, T-stage, lymph node involvement, and presence of lymphovascular or perineural invasion, the negative prognostic value of high ERCC1 expression persisted on multivariate Cox regression analysis (HR 2.5; 95%CI: 1.03-6.0; p=0.04). By contrast, in patients who underwent resection only (n=35), high ERCC1 expression was associated with improved OS (40.4 vs 12.7mos; p=0.10; Figure). This finding persisted on multivariate analysis (HR 0.20; 95%CI: 0.04-.86; p=0.03). Conclusion: Resected gastric adenocarcinoma exhibits differential expression of TS and ERCC1. TS expression is not associated with OS. However, similar to what is reported in lung cancer, high ERCC1 tumor expression is associated with decreased OS in patients receiving chemotherapy, but is associated with increased OS in those treated with surgery alone. ERCC1 expression has prognostic value in resected gastric cancer and further investigation is warranted.



P321

Cardioesophageal and Esophageal Cancer: Optimization of Management O. Kshivets.* *surgery, Kachkanar Hospital, Kachkanar, Russian Federation.*

OBJECTIVE: Search of best treatment plan for cardioesophageal/esophageal cancer (CEC) patients (CECP) was realized. METHODS: We analyzed data of 411 consecutive CECP (age=55.6±8.7 years; tumor size=6.7±3.3 cm) radically operated (R0) and monitored in 1975-2012 (m=307, f=104; esophagogastrectomy- EG Garlock=271, EG Lewis=140, combined EG with resection of pancreas, liver, diaphragm, colon transversum, lung, trachea, pericardium, splenectomy=127; adenocarcinoma=216, squamous=185, mix=10; T1=62, T2=99, T3=141, T4=109; N0=170, N1=57, M1A=184, G1=116, G2=98, G3=197; early CEC=43, invasive=368; esophageal cancer=139, cardioesophageal cancer=272): only surgery-S=327, adjuvant treatment-AT=84 (chemoimmunoradiotherapy=36: 5-FU+thymalin/taktivin +radiotherapy 45-50Gy, adjuvant chemoimmunotherapy=48). Cox modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence. RESULTS: For total of 411 CECP overall life span (LS) was 1632.2±2141.6 days, (median=783 days) and cumulative 5-year survival (5YS) reached 40.1%, 10 years – 32.9%, 20 years – 24%. 102 CECP lived more than 5 years without CEC progressing. 216 CECP died because of CEC during the first 5 years after surgery. 5YS was superior significantly after AT (61.7%) compared with S (36.2%) (P=0.000 by log-rank test). Cox modeling displayed that 5YS significantly depended on:

phase transition (PT) early-invasive CEC in term of synergetics, PT N0-N1M1A, AT, cell ratio factors (P=0.000-0.038). Neural networks computing, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT early-invasive CEC (rank=1), PT N0-N1M1A (rank=2), AT (3), segmented neutrophils/cancer cells-CC) (4), lymphocytes/CC (5), monocytes/CC (6). Correct prediction of 5YS was 100% by neural networks computing. CONCLUSIONS: Optimal management strategies for CECP are: 1) screening and early detection; 2) availability of experienced thoracoabdominal surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymphadenectomy for completeness; 4) high-precision prediction; 5) adjuvant treatment for CECP with unfavorable prognosis.

P322

Results of Positron Emission Tomography in Pancreatic Cancer: Routine Use is Not Justified A.R. Bhama,* B.E. Johnson, Y. Menda, J.R. Howe, S.K. Bhatia, J.J. Mezhir. *Surgery, University of Iowa, Iowa City, IA.*

Introduction: Positron emission tomography (PET) is commonly performed in the evaluation of patients with pancreatic cancer. To date, there are little data to support or refute the use of this costly imaging modality. In the era of modern imaging with computed tomography (CT), we set out to evaluate the impact of PET scans on the management of patients with pancreatic cancer. Methods: A review of patients with pancreatic cancer who had a PET scan at any time during the treatment of their disease was performed. Clinicopathologic variables were reviewed and the impact of the PET scan on treatment was determined, which was defined as a change in the treatment plan based on PET results. Results: 62 patients with pancreatic cancer had a PET scan from 6/04-5/12. There were 14 patients (22.6%) who underwent formal pancreatectomy while the remaining 48 patients did not, due to: disease progression during neoadjuvant treatment (n=26, 54.2%), the diagnosis of metastasis (n=17, 35.4%), or poor performance status (n=5, 10.4%). At a median follow-up of 12.1 months (range 1-41), 52 patients died (median survival for the cohort=10.3 months, range 1-40 months) Indications for PET included staging prior to neoadjuvant therapy (n=34, 54.8%), initial staging of disease (n=21, 33.9%), or staging prior to initiation of adjuvant therapy (n=7, 11.3%). Upon review, PET results changed the treatment plan in 6 patients (9.7%). Of the 6 patients, 2 patients were being evaluated for neoadjuvant chemoradiation (2/34, 5.9%), and 4 patients had a PET scan as part of their staging workup (4/21, 19%). These 6 patients where PET altered management were found to have liver metastasis not seen on CT. There were 2 patients who had invasive procedures due to findings on PET, and both had benign findings (one sinus biopsy, one colonoscopy). Conclusions: These data suggest that the routine use of PET scan, particularly for treatment planning in patients with locally advanced pancreatic cancer, is of limited value. PET scans may help in the treatment planning of select patients with advanced pancreatic cancer where findings of distant disease would spare patients aggressive local therapy.

Impact of PET scan on Management of Patients with Advanced Pancreatic Cancer<b?>

Clinical Scenario	n (%)
Staging Prior to Adjuvant Therapy	0/7 (0)
Staging Prior to Neoadjuvant Therapy	2/34 (5.9)
Part of Initial Staging Workup	4/21 (19)
Total Patients Impacted by PET Results	6/62 (9.7)

P323

Aggressive Locoregional Management of Gastric Peritoneal Carcinomatosis D. Magge,* A. Mavanur, J.F. Pingpank, M.P. Holtzman, A.H. Zureikat, L. Ramalingam, H.L. Jones, K.K. Lee, H.J. Zeh, D.L. Bartlett, H.A. Choudry. *University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Peritoneal carcinomatosis from gastric cancer (GPC) responds poorly to systemic chemotherapy. However, limited published data demonstrate improved outcomes after aggressive locoregional therapies. We assessed the efficacy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) in GPC. Methods: We prospectively analyzed perioperative and oncologic outcomes in 23 patients with GPC undergoing CRS/HIPEC between 2002 and 2011. Kaplan Meier survival curves and multivariate Cox-regression models were used to identify prognostic factors affecting oncologic outcomes. One patient was lost to follow-up and was excluded from survival analyses. Results: CRS/HIPEC was performed for synchronous GPC in 20 patients and metachronous GPC in 3 patients. Complete CRS was achieved in 22 patients (CC-0/No macroscopic residual tumor=17; CC-1/Residual tumor nodules < 2.5 mm) and median peritoneal carcinomatosis index was 11 (IQR 7-16). Most patients received preoperative chemotherapy (78%) and total gastrectomy (78%), while 39% received adjuvant chemotherapy. Pathology revealed diffuse histology (65%), poor differentiation (78%), signet ring cells (65%) and lymph node involvement (61%). The median hospital and ICU lengths of stay were 20 (IQR 13-24) and 2 (IQR 1-4) days. Major postoperative morbidity occurred in 12 patients (52%), with 1 in-hospital mortality at POD 66. With a median follow-up of 52 months, median overall survival was 9.4m (95% CI 0-19.7), with 1- and 3- year overall survival (OS) rates of 46% and 9%. One patient survived longer than 5 years despite aggressive histology. Median progression-free survival (PFS) was 7m (95% CI 0-20.2). In a multivariate Cox-regression model, male gender (HR 3.3), inadequate cytoreduction with residual tumor nodules > 2.5mm (HR 2.6), two or more involved lymph nodes (HR 2.6) and greater than two intestinal anastomoses (HR 1.7) were joint significant predictors of poor OS (Chi-square=10.6, p=0.03). Conclusions: Aggressive CRS/HIPEC for GPC may confer a survival benefit in a highly selected group of patients with limited lymph node involvement and completely resectable disease requiring fewer extensive visceral resections.

P324

Impact of Neoadjuvant Chemoradiotherapy on Postoperative Course after Curative Intended Transthoracic Esophagectomy in Esophageal Cancer Patients D. Bosch,[1] C.T. Muijs,[2] G.A. Hospers,[3] J.C. Beukema,[2] V.E. Mul,[2] J.T. Plukker.[1]* *1. Dept Surgical Oncology, University Medical Center Groningen, Groningen, Groningen, Netherlands; 2. University Medical Center Groningen: dept of radiotherapy, Groningen, Groningen, Netherlands; 3. University Medical Center Groningen: dept of med.oncology, Groningen, Groningen, Netherlands.*

Impact of neoadjuvant chemoradiotherapy on postoperative course after curative intended transthoracic esophagectomy in esophageal cancer patients. Background: Neoadjuvant chemoradiotherapy (CRT) improves loco-regional control and overall survival in esophageal cancer patients. Although relatively low adverse events are encountered during neoadjuvant CRT, severe postoperative side-effects may occur leading to increased morbidity and even mortality. Therefore, we investigated the impact of a currently used preoperative CRT regimen of 41.4Gy/5wks radiotherapy with concurrent Carboplatin and Paclitaxel (CROSS scheme) on the postoperative course. Patients and methods: Between 2006 and 2012, a total of 96 patients (staged cT1N+/T2-4a/N0-3 and M0, both adeno- and squamouscell ca.) were treated neoadjuvantly according to the above scheme. These patients were matched with 96 patients who underwent surgery alone, from a prospectively maintained database on: gender, age, comorbidity (diabetes mellitus, hypertension, angina pectoris, heart failure, myocardial infarction, COPD, TIA/CVA), ASA classification and side of thoracotomy. Results: Surgical mortality (90-day and/or in-hospital mortality) and 30-day mortality did not differ between both groups. In the neoadjuvant treated group significant more patients were diagnosed with a pneumonia (51% vs 27.1%; p=0.001), pleural effusion (25% vs 13.5%; p=0.044) and arrhythmias (34.4% vs 20.4%; p=0.008). Besides, in the multivariate analyses neoadjuvant CRT was significantly associated with an increased risk of pneumonia (p=0.000 odds ratio 3,267) and arrhythmia (p=0.012 odds ratio 2,617). Despite these outcomes, no differences were detected in ICU - and in hospital stay. Conclusions: In this study, the observed increase of postoperative respiratory events and arrhythmia in the neoadjuvant CRT group has no effect on hospital or ICU stay and mortality. However, further research is warranted on limitation of radiation-induced cardiopulmonary toxicity.

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Predictors for Readmission after Pancreatic Resection for Malignancy N.A. Newman,[1]* J.T. Lucas, Jr,[2] D.A. Peacock,[2] P.A. Trottman,[1] S.S. Wentworth,[1] S.M. Winters,[1] E. Levine,[1] P. Shen.[1] *1. Wake Forest University Department of Surgical Oncology, Winston-Salem, NC; 2. Wake Forest University Department of Radiation Oncology, Winston-Salem, NC.*

Introduction Readmission after pancreatic resection has been reported as high as 50%. This study was undertaken to determine factors predicting readmission after pancreatic resection for malignancy. Methods We reviewed the medical records of 202 patients to identify patients that had a pancreatic resection for malignancy between 2003 and 2010. Outcome measures included patient characteristics, medical comorbidities, and perioperative factors. Results A total of 202 patients underwent pancreatic resection for malignancy. AJCC T stage was T1, T2, T3, and T4 in 10.9, 26.3, 52 and 9.2% respectively. Pancreatic head malignancies made up 84.8% of the patients, while 8.4% were pancreatic body malignancies, 2.3% were pancreatic neck, and 4.5% were pancreatic tail malignancies. Preoperative biliary stents were placed in 58% of patients. Adjuvant radiation and chemotherapy were given in 47.8 and 61.39% respectively. The readmission rate following resection was 20% at 60 days. The most common reasons for readmission within 60 days were delayed wound healing and renal insufficiency. On univariate analysis, factors predicting higher readmission rates included positive retroperitoneal margin (p=0.048), delayed gastric emptying (p=0.015), and presence of wound infection (p=0.0020). Conclusion Factors related to tumor burden and GI/infectious complications were the most common predictors of readmission after pancreatic resection for malignancy. Though tumor size is generally an immutable variable, improved management of postoperative complications remains an important factor in decreasing readmission rates after pancreatic resection for malignancy.

P326

Comparative Benefits of Nab-Paclitaxel over Gemcitabine or Polysorbate-based Docetaxel 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.*

Background: Gemcitabine (Gem), a standard cytotoxic therapy for pancreatic cancer, has shown limited clinical benefits. Nanoparticle albumin-bound (nab) paclitaxel (NPT), 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 the NPT treatment benefits compared with Gem or solvent-based taxane docetaxel (DT) in experimental pancreatic cancer. Methods: In vitro cell proliferation and protein expression were measured by WST-1 assay and immunoblotting. Tumor growth and animal survival studies were performed in murine xenografts. Intratumoral proliferative activity was measured using Ki67 nuclear antigen staining. Results: For AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells in vitro, Gem IC50 levels were 23.9 μM, 506 nM, 332 nM and 14.5 nM; DT IC50 levels were 30 nM, 4.6 nM, 37.5 nM and 27 nM; and NPT IC50 levels were 7.6 μM, 208 nM, 519 nM and 526 nM. NPT addition decreased Gem IC50 to 1.7 μM, 189 nM, 123 nM and 913 nM; DT addition decreased Gem IC50 to 436 nM, 470 nM, 124 nM and 0.2 nM in AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1 cells, respectively. NPT and DT treatment increased stathmin phosphorylation and decreased tubulin expression in vitro. In a heterotopic in vivo model, net tumor growth inhibition after Gem, DT and NPT was 67, 31 and 72 percent, while intratumoral proliferative index inhibition was 41, 53 and 68 percent, respectively. In an intraperitoneal model, median animal survival was significantly longer in the NPT treatment group (41 days, p<0.002 vs. control and Gem) compared to Gem (32 days, p=0.005 vs. control), DT (32 days, p=0.005 vs. control) and controls (20 days). Animal survival in NPT-Gem and DT-Gem sequential treatment groups was 43 and 40 days, and thus not superior to NPT alone. Conclusions: Nab-paclitaxel has significantly superior antitumor activity as a single agent in experimental pancreatic cancer compared with gemcitabine or docetaxel. These findings provide a strong rationale for considering nab-paclitaxel as first-line monotherapy in patients with pancreatic cancer.

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Prognostic Value of Response to Neoadjuvant Therapy in Patients with Stage II and III Esophageal Cancer C. Rosati,[1]* V.P. Koshenkov,[2] A.T. Prescott,[2] M.E. Freiser,[2] T. Koru-Sengul,[3] J.L. Sparling,[2] D. Franceschi.[2] *1. Department of General Surgery, University of Pisa, Pisa, Italy; 2. Department of Surgery, Jackson Memorial Hospital/University of Miami, Miami, FL; 3. Department of Epidemiology and Public Health, University of Miami, Miami, FL.*

Background: Response to neoadjuvant therapy could significantly impact long-term survival for patients with esophageal cancer. Methods: We retrospectively analyzed survival data for all patients with clinical stage II and III esophageal cancer who underwent neoadjuvant chemotherapy (neoCT) or chemoradiotherapy (neoCT+RT) and subsequent resection at a tertiary care referral center from 1/2000-6/2012. Response to neoadjuvant therapy was defined as downstaging from initial (clinical) to final (pathologic) stage. Results: Among 279 patients who met inclusion criteria, 84 (30%) had clinical stage II and 195 (70%) stage III esophageal cancer. NeoCT was administered to 63 (75%) and 151 (77%) patients respectively, while neoCT+RT was given to 21 (25%) and 44 (23%) patients, respectively (p=0.66). At univariate analysis, neither initial stage nor type of neoadjuvant therapy were predictors of long term survival (log-rank test, p=0.09 and p=0.47, respectively). On the contrary, responders (n=142) to neoadjuvant treatment had a significantly better survival than nonresponders (n=137) (median survival 121 and 33 months, respectively; log-rank test, p<0.0001; Figure 1 a-b). For initial stage II patients, median survival was significantly better (p=0.003) for responders to neoCT (135 months) or neoCT+RT (95 months) than for non responders (52 and 38 months, respectively). A similar trend was noticed for initial stage III patients (median survivals: 121 and 122 months for responders to neoCT or neoCT+RT, respectively; 27 and 16 months for nonresponders to neoCT or neoCT+RT, respectively; p<0.0001). Response to neoadjuvant therapy was associated with better survival even when stratifying patients according to the type of neoadjuvant therapy received (p<0.0001). Multivariate analysis demonstrated age (p<0.001) and response to neoadjuvant therapy (p<0.001) to be the only factors predictive of long-term survival. Conclusion: Initial stage (II vs. III) or type of neoadjuvant therapy (chemotherapy vs. chemoradiation therapy) were not predictors of patient survival. On the contrary, response to neoadjuvant therapy was significantly associated with improved long-term survival.

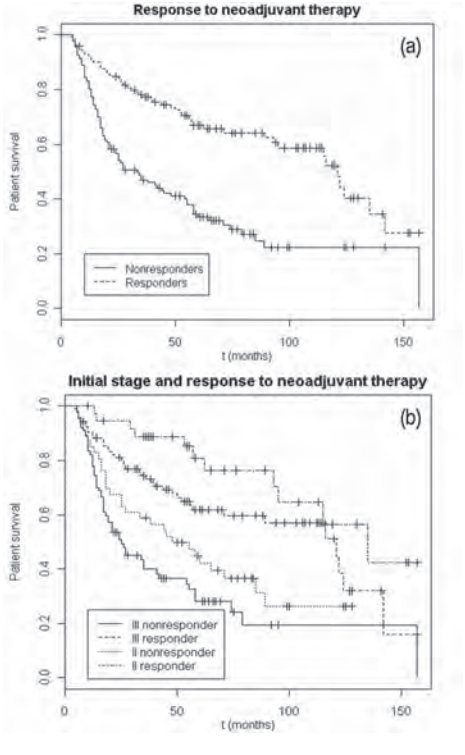

Figure 1

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