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ABSTRACTS

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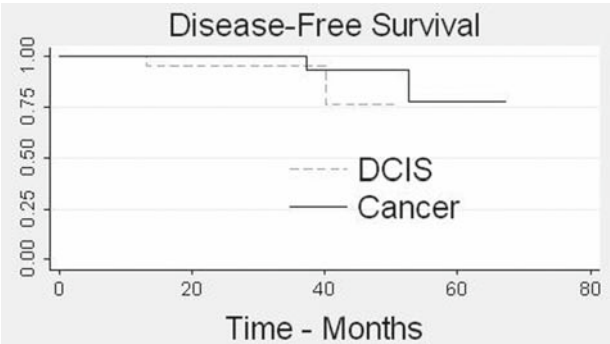
Can We Eliminate Radiotherapy After Breast Conservation Therapy?-Results Of A Phase II Trial of eRFA V. Klimberg,* B.D. Badgwell, L.L. Adkins, M. Smith, S. Korourian. *Surgery, University of Arkansas for Medical Sciences, Little Rock, AR.*

Introduction: Margin status is the only prognostic factor that surgeons can affect yet 75 to 90% of local recurrence (LR) is at the tumor bed even after XRT. We hypothesized that excision followed by radiofrequency thermal ablation (eRFA) to extend the margin by 1cm can provide similar therapeutic benefit to XRT. Hence we proceeded with the current pilot study to determine if creating an additional in vivo 1cm tumor-free zone around the cavity bed with RFA can decrease LR and possibly obviate the need for XRT in early breast cancer. Methods: Between 7/02-2/08 we conducted a Phase II trial of RFA in women desiring lumpectomy. After removal of the cancer with surgical lumpectomy, an RFA probe was deployed 1 cm circumferentially into the lumpectomy cavity and maintained at 100°C for 15 minutes. Intraop doppler was used to follow the margin ablation.These patients did not receive XRT but did receive systemic therapy. Patients were followed for local recurrence and cosmesis. Results: 94 pts (mean age:66.68years±11.01SD), 62 invasive, 32 DCIS, tumor size of 1.0cm±0.8cm,S.D. 48 with grade I, 26 with grade II, 19 with grade III, and one unknown underwent intra-op eRFA. 24 patient had inadequate margins (≤2mm) including 8 grossly positive and four focally positive margins. Eight patients underwent reresection and were excluded. With a mean follow-up of 23 months±15 months (6-67 months) no LRs in the tumor bed were seen. There were four elsewhere recurrences – 3 ipsilateral and 1 contralateral. DFS is shown in the Figure. Two week Cosmesis was scored in 56 patients rating 26 excellent, 22 good, and 8 fair. Conclusion: Short-term follow-up suggests that in pts with early breast cancer eRFA can reduce LR without the need for or complications of XRT. eRFA may represent a new paradigm in achieving optimal breast conservation without XRT.



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Zic1 Over Expression is Oncogenic in Dedifferentiated Liposarcoma E.R. Brill,* B. Laxa, M. Lagos-Quintana, P. DeCarolis, R. O'Connor, R. Gobble, C. Angeles, S. Singer. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Zic1, a gene essential for proper neurologic development, has surprisingly been shown to be one of the most highly expressed genes in dedifferentiated (DD) liposarcoma (LS) compared to normal fat (NF). In order to elucidate the role of Zic1 over expression in sarcomagenesis, we investigated its cellular and biochemical functions in two DD LS cell lines. Affymetrix U133A microarray analysis was performed on 64 DD LS and 18 NF tissue patient samples. Zic1 over expression was validated by RT-PCR in DD LS tissue samples and in two DD LS cell lines, DDLS8817 (DLS) and LPS141 (LPS), and compared to NF and adipose-derived stem cells (ADSC). To study its oncogenic properties, we used shRNA lentiviral constructs to knockdown Zic1 expression in the DD LS cell lines and measured cell proliferation in these knockdowns with a CyQuant assay. RT-PCR was used to measure potential downstream targets of Zic1, p27 and Wnt7a. We found a 36-fold increase in Zic1 expression in DD LS compared to NF tissues by U133A analysis (FDR<1x10-7). The LS cell lines, DLS and LPS, were also found to over express Zic1 by 4.6 (p=0.002) and 3.8 (p=0.002) fold, respectively, compared to ADSC by RT-PCR. The shRNA lentivirus knockdown was able to reduce Zic1 expression in both DD LS cell lines to levels present in ADSC. Following Zic1 knockdown, both DD LS cell lines demonstrated a reduction in proliferation compared to their non-infected and scramble controls, 55% and 52% for DLS (p<0.0001), and 62% and 48% for LPS (p<0.0001), respectively, at three days after plating for CyQuant assay. Following Zic1 knockdown, p27 increased by 45% (p=0.003) and 100% (p=0.001) in DLS, and by 102% (p=0.01) and 75% (p=0.03) in LPS, compared to their non-infected and scramble controls. In addition, in the LPS Zic1 knockdown, Wnt7a increased 4-fold compared to its non-infected, scramble and GFP controls (p=0.02). We have shown that Zic1 expression is essential for proliferation and survival of DD LS cell lines. This effect is partly mediated through the decreased expression of the cell cycle regulators, p27 and Wnt7a. Understanding the mechanisms involved in Zic1 mediated oncogenesis will enable the development of new targeted therapies for DD LS.

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The value of FDG-PET for hepatic surgery of colorectal liver metastases: a multicentre randomized clinical study T. Ruers,[1]* B. Wiering,[2] P. Krabbe,[2] J. Van der Sijp,[3] R. Roumen,[4] K. De Jong,[5] E. Comans,[3] J. Pruim,[5] H. Dekker,[2] W. Oijen.[2] *1. Surgery, NKI/AVL, Amsterdam, Netherlands; 2. Radboud Medical Centre NIjmegen, NIjmegen, Netherlands; 3. VUmc Amsterdam, Amsterdam, Netherlands; 4. MMC Veldhoven, Veldhoven, Netherlands; 5. UMC Groningen, Groningen, Netherlands.*

Background With the increasing possibilities for surgical treatment of colorectal liver metastases, careful selection of patients who may benefit from surgical treatment becomes critical. Staging by positron emission tomography (PET) with 18-fluorodeoxyglucose (18FDG) is thought to improve conventional staging by CT. Up to now, however, randomized controlled trials (RCT) showing that the addition of FDG-PET leads to superior clinical results and improved clinical management in these patients are lacking. In this first RCT we investigated whether the addition of FDG-PET to the work up of patients with colorectal liver metastases is beneficial and reduces the number of futile laparotomies. Methods. 150 patients with colorectal liver metastases selected for surgical treatment by imaging with CT scan were randomly assigned to CT imaging only (n=75) or CT imaging plus FDG-PET (n=75). Follow up was performed for at least 3 years. Outcome measures were the number of futile laparotomies, disease free and overall survival. Futile laparotomy was defined as any laparotomy that did not result in complete tumour treatment, that revealed benign disease or that did not result in a disease free survival period longer than 6 months. Results. Demographics, patient and tumour characteristics were similar for both groups.. The number of futile laparotomies was 34 (45%) in the control arm without FDG-PET and 21 (28%) in the experimental arm with FDG-PET, the relative risk reduction for futile laparotomy was 38% (95% CI = 4-60, P= 0.042). Thee year overall and disease free survival were comparable between both groups Conclusion. This RCT shows that the addition of FDG-PET to the work-up for surgical resection of colorectal liver metastases prevents unnecessary surgery in one out of six patients. In the group randomized for FDG-PET, this improved selection was not counterbalanced by a decrease of overall or disease free survival.

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Targeting N-cadherin to Enhance Cytotoxicity of Melphalan in Regional Chemotherapy: Final Results of a Phase I Study of Systemic ADH-1 in Combination with Melphalan via Isolated Limb Infusion (M-ILI) in Patients (pts) with Locally Advanced In-transit Malignant Melanoma G.M. Beasley,[1]* N. McMahon,[1] G. Sanders,[1] C.K. Augustine,[2] P. Zipfel,[2] J. Padussis,[1] M.A. Selim,[3] W. Petros,[4] B. Peterson,[5] M. Lawton,[6] R. Norris,[6] W.P. Peters,[6] M.I. Ross,[7] D.S. Tyler.[1] *1. Duke University, Dept. of Surgery, Durham, NC; 2. VA Medical Center, Durham, NC; 3. Duke University, Dept. of Pathology, Durham, NC; 4. West Virginia University, Dept. of Basic Pharm. Sciences, School of Pharmacy and Cancer Ctr, Morgantown, WV; 5. Duke University, Dept. of Biostatistics and Bioinformatics, Durham, NC; 6. Adherex Technologies, Inc., Durham, NC; 7. University of Texas MD Anderson Cancer Center, Dept. of Surgery, Houston, TX.*

Background: M-ILI is a well tolerated treatment for pts with in-transit melanoma of the extremity with a 30% CR rate in our own cohort of treated pts. ADH-1 is a cyclic pentapeptide that disrupts N-cadherin adhesion com-

plexes and when given systemically in a preclinical model of regional melphalan therapy demonstrated synergistic antitumor activity. Methods: A multicenter Phase I dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of systemic ADH-1 in combination with M-ILI in pts with measurable in-transit melanoma of the extremity was performed. The phase I ADH-1 dose escalation cohorts of 3 pts each were 1000, 2000, and 4000 mg administered intravenously on Days 1 and 8 in combination with standard dose M-ILI corrected for ideal body weight (IBW) on Day 1. The 4000 mg ADH-1 cohort was expanded to include 10 total pts. N-cadherin IHC staining and qPCR analysis were performed on pretreatment tumor tissue. Response was defined at 3 months using modified RECIST. Results: Sixteen pts, including 8 previous M-ILI alone, have been treated with no observed DLTs. Common treatment related grade 1/2 toxicities included skin/dermatologic (n=14), pain (n=12), and nausea (n=6). There were 5 Grade 3 toxicities and 1 Grade 4 CPK elevation. In field responses of the 16 pts determined at the 3 month post treatment time point included 8 CRs, 2 PRs, 2 SD, and 4 PDs. Of 6 CRs now 6 months post-treatment, 4 have maintained a CR. IHC and qPCR analysis demonstrated N-cadherin expression in 13/16 of patients. PK analysis demonstrated increasing ADH-1 concentrations at each dose escalation and minimal variability in melphalan drug levels across pts. Conclusion: Systemic ADH-1 at a dose of 4000 mg on Day 1 and 8 in combination with M-ILI on Day 1 is a novel targeted therapy approach to optimize regional therapy of advanced melanoma. Tumor responses, especially the 50% CR rate, exceeded expectations in this group of heavily pretreated pts.

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Factors Associated with False-Negative Sentinel Lymph Node Biopsy in Melanoma Patients: Results from a Prospective Randomized Trial C.R. Scoggins,[1]* R.C. Martin,[1] M.I. Ross,[2] M.J. Edwards,[3] D.S. Reintgen,[5] M.M. Urist,[4] K.M. McMasters.[1] *1. Surgery, University of Louisville, Louisville, KY; 2. MD Anderson Cancer Center, Houston, TX; 3. University of Cincinnati, Cincinnati, OH; 4. University of Alabama at Birmingham, Birmingham, AL; 5. Lakeland Regional Cancer Center, Lakeland, FL.*

Introduction: Some melanoma patients who undergo sentinel lymph node (SLN) biopsy will have false-negative (FN) results. We sought to determine the factors and outcomes associated with FN SLN biopsy in melanoma patients. Methods: Analysis was performed of a prospective multi-institutional study that included patients with cutaneous melanoma ≥1.0 mm Breslow thickness that underwent SLN biopsy. FN results were defined as recurrence in a nodal basin previously determined to have tumor-negative SLN. Kaplan-Meier survival analysis, univariate and multivariate analyses were performed. Results: This analysis included 2451 patients with a median follow-up of 61 months. FN, true-positive (TP), and true-negative (TN) SLN results were found in 59 (2.4%), 486 (19.8%), and 1906 (77.8%) patients, respectively. On univariate analysis comparing the FN to TP groups, respectively, the following factors were significantly different: age (52.6 vs. 47.6 yrs, p=0.004), Breslow thickness (mean 2.1 vs. 3.1 mm, p=0.003), lymphovascular invasion (LVI; 3.7% vs. 13.7%, p=0.037), and local/in-transit recurrence (LITR; 32.2% vs. 12.4%, p<0.0001); these factors remained significant on multivariate analysis. Overall 5-year survival was significantly greater in the TN group (86.7%) compared to the TP (62.3%) and FN (51.3%) groups (p<0.0001); however, there was no significant difference in overall survival comparing the TP and FN groups (p=0.32). Conclusions: This is by far the largest study to evaluate the FN SLN results in melanoma patients. FN results are associated with greater patient age, lower mean Breslow thickness, less frequent LVI, and a greater risk of LITR. However, survival of patients with FN SLN is not significantly worse than those with TP SLN.

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Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Interim results of a randomised phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC) T. Ruers,[1]* F. Van Coevorden,[1] J. Pierie,[2] I. Borel Rinkes,[3] C. Punt,[4] J. Ledermann,[5] G. Poston,[9] W. Bechstein,[6] M. Lentz,[8] M. Mauer,[10] B. Nordlinger.[7] *1. Surgery, NKI/AVL, Amsterdam, Netherlands; 2. medical centre leeuwarden, leeuwarden, Netherlands; 3. University Medical Centre Utrecht, Utrecht, Netherlands; 4. Radboud University Medical Centre, Nijmegen, Netherlands; 5. Middelsex Hospital – Meyerstein Institute, London, United Kingdom; 6. Johann Wolfgang Goethe-University, Frankfurt am Main,, Germany; 7. CHU Ambroise Paré, Boulogne-Billancourt, France; 8. EORTC Data Center, Data Management Unit,, Brussels, Belgium; 9. Royal Liverpool University Hospital,, Liverpool, United Kingdom; 10. EORTC Data Center, Statistics Department, Brussels, Belgium.*

Background: In pts with a limited number of unresectable CRC LM there is an increasing tendency to combine systemic chemotherapy (CT) with local tumour destruction by RFA. However, the benefit of this combined treatment has not been proven. Methods: This study evaluated the addition of RFA to systemic CT in patients with unresectable CRC LM up to 9 lesions and without extrahepatic disease. Between 2002 and 2007, 119 pts were randomised between CT alone (59) or RFA plus CT (60) In both arms, CT consisted of 6 months FOLFOX (oxaliplatin 85mg/m2 and LV5FU2) plus, since October 2005, bevacizumab. Primary endpoint was overall survival (OS) at 30 months. Safety, OS and progression free survival (PFS) were secondary endpoints. Results: Baseline characteristics were similar between arms: 60% had ≥ 4 LM. In the RFA + CT arm, 30 pts (52.6%) received RFA alone, while in 27 pts RFA (47.4%) was combined with resection. 51 patients (85%) in the RFA+CT arm received CT compared to all 59 in the CT arm. The median number of chemotherapy cycles for patients who received CT was 10 in both arms. Toxicity profiles for CT were comparable between both arms. Post-operative complications were observed in 10 cases after RFA (33%) and in 9 cases (33%) after RFA plus resection. Major complications were cardiac failure (3), hemorrhage (2) and infection (6), 3 patients needed re-operation. Minor complications were fever (12) and fatigue (6). There was one post-operative death (1.8%). One year PFS is 39.35% (95% CI 26.78-51.67) in the CT arm versus 60.06% (46.24-71.40) in the RFA+CT arm (overall log-rank P=0.0267). At present interim analysis, median PFS is 10 mo in the CT arm versus 16.8 mo in the RFA + CT arm. The number of patients with local recurrence at the RFA site only was 5. Conclusion: This is the first study that prospectively investigates the efficacy of RFA in combination with CT. In pts with unresectable colorectal liver metastases RFA +CT is safe and improves PFS compared to CT alone.

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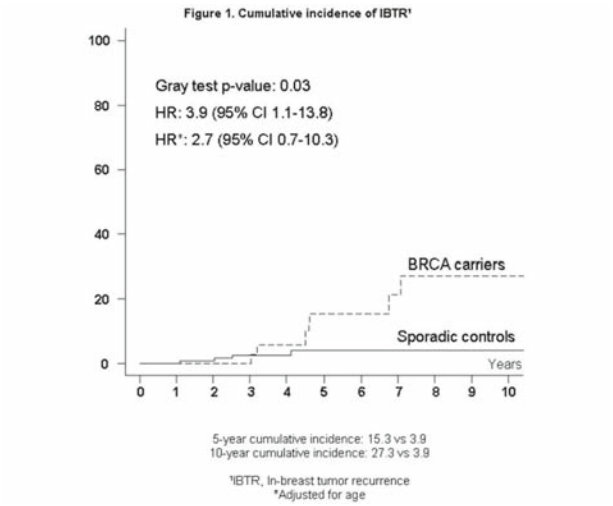
Conservative Management of Breast Cancer in BRCA1/2 Mutation Carriers C.A. Garcia-Etienne,[1]* M. Barile,[2] O.D. Gentilini,[1] E. Botteri,[3] N. Rotmensz,[3] G. Farante,[1] A. Luini,[1] B. Bonanni.[2] *1. European Institute of Oncology, Department of Breast Surgery, Milan, Italy; 2. European Institute of Oncology, Department of Cancer Prevention and Genetics, Milan, Italy; 3. European Institute of Oncology, Department of Epidemiology and Biostatistics, Milan, Italy.*

INTRODUCTION: About 5 to 10% of breast cancer patients treated with breast-conserving surgery (BCS) will develop in-breast tumor recurrence (IBTR). Recent data from multi-institutional studies have shown an increased risk of IBTR after BCS for BRCA1/2-associated breast cancer. We report the outcome of BCS in BRCA mutation carriers followed at a single institution. METHODS: A total of 54 women with BRCA1/2-associated breast cancer treated with BCS and radiotherapy were matched for age, tumor size, and time of surgery with 162 controls with sporadic breast cancer who had the same treatment. The control group had a negative family history for breast cancer. Primary end-points were cumulative incidence of IBTR and contralateral breast cancer (CBC). RESULTS: Median age (range) was 36 (22-53) and 37 (23-55) years for mutation carriers and controls, respectively; mean tumor size was 1.8 cm in carriers and 1.9 cm in controls. All patients were operated between 1994 and 2007. Tumor histology was invasive ductal carcinoma in 76% of mutation carriers and in 85% of controls. Median follow-up was 4 years for both groups. IBTR was observed in 6 of 54 mutation carriers and in 4 of 162 sporadic controls. Ten-year cumulative incidence of IBTR was 27% for mutation

carriers and 4% for sporadic controls (P-value = 0.03, Fig. 1), with an age-adjusted HR of 2.7 (95% CI, 0.7-10.3). Ten-year cumulative incidence of CBC was 25% for mutation carriers and 2% for sporadic controls (P = 0.03). Incidence curves for IBTR and CBC were not modified when carriers who had undergone oophorectomy (n = 16) were removed from the analysis. There was 1 (1/54) regional recurrence in a mutation carrier as a supraclavicular node and 2 (2/162) in the control group as isolated axillary metastasis. Two (2/54) patients presented distant metastasis among carriers and 6 (6/162) among controls. CONCLUSIONS: Our data suggest that IBTR risk after BCS in BRCA mutation carriers is increased compared to patients who present sporadic breast cancer. Likewise, the rate of CBC after surgery seems to be increased in this group. These risks should be discussed with this subset of patients when choosing treatment options and risk-reduction strategies.



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Laparoscopic Left Pancreatectomy: Complication Risk Score Predicts Morbidity and Risk for Pancreatic Fistula S.M. Weber,[1]* C.S. Cho,[1] D. Bentrem,[2] A. Nakeeb,[3] M. Schmidt,[3] N. Merchant,[4] A.A. Parikh,[4] R.C. Martin III,[5] C.R. Scoggins,[5] S. Ahmad,[6] H.J. Kim,[7] N. Hamilton,[8] W. Hawkins,[8] D.A. Kooby.[9] *1. University of Wisconsin, Madison, WI; 2. Northwestern University, Chicago, IL; 3. Indiana University, Indianapolis, IN; 4. Vanderbilt University, Nashville, TN; 5. University of Louisville, Louisville, KY; 6. Cincinnati University, Cincinnati, OH; 7. University of North Carolina, Chapel Hill, NC; 8. Washington University, St. Louis, MO; 9. Emory University, Atlanta, GA.*

Introduction: Laparoscopic left pancreatectomy (LLP) is being performed with increasing frequency with a poor understanding of the risk factors for complications. A prior study from our group showed complication rates are lower following LLP than open left pancreatecomy. We evaluated factors contributing to patient morbidity after LLP. **Methods:** Records from patients undergoing LLP from 2000 to 2008 from 9 academic medical centers were evaluated to assess risk factors for perioperative (30d) complications. Extent of pancreatic resection was determined by the length of the gross pancreatic specimen. Complications and pancreatic fistula rates were assessed according to previously defined criteria (Dindo et al, Bassi et al). A model was developed to predict patients at increased risk for complications. **Results:** Of 219 LLP analyzed, indications included cystic neoplasms in 122 (56%), solid neoplasms in 83 (38%), and chronic pancreatitis in 14 (6%). Overall morbidity and mortality (30d) occurred in 39% and 0%, respectively. Pancreatic fistulae were detected in 23%, with major fistulae seen in 10%. Major complications occurred in 23 (11%) patients, including 10 pancreatic fistulae, 3 pulmonary emboli, 2 pleural effusions, and 8 others. On multivariate analysis including transection type, ASA class, tumor size, splenectomy, BMI, length of resected pancreas, and EBL, only BMI, length of resected pancreas, and EBL were associated with an increased likelihood of major complications and major fistulae. A complication risk score consisting of 1 point each for BMI >27, pancreatic specimen length >8 cm, or EBL ≥ 150 cc predicted an increased risk of any complication, major complication, any pancreatic fistula, and major pancreatic fistula (Table). **Conclusion:** This series, the largest analysis of LLP, reveals the overall risk of complications following LLP is 39%, with major pancreatic fistulae occurring in 10%. A Complication Risk Score incorporating BMI, extent of pancreatic resection, and EBL correlates with all endpoints evaluated. The Complication Risk Score should be utilized when quality outcome measures are evaluated.

Complication Risk Score	Any complication	Major complication	Any pancreatic fistula	Major pancreatic fistula
0	13%	3%	3%	0
1	35%	2%	19%	2%
2	46%	14%	31%	13%
3	57%	30%	37%	30%
p value	0.002	<0.0001	0.006	<0.0001

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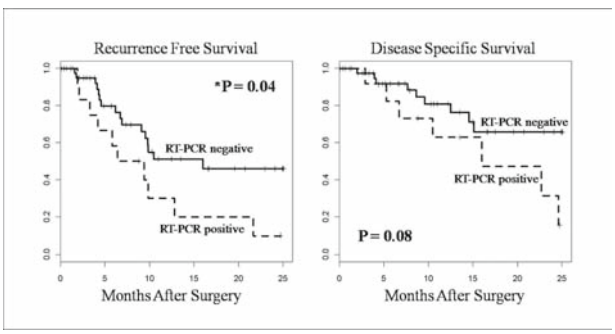
Prognostic impact of RT-PCR based detection of peritoneal micrometastases in pancreatic cancer patients undergoing curative resection K.J. Kelly,* K. Moore Dalal, J. Wong, R. Gladdy, Y. Woo, M. Gonen, P. Allen, Y. Fong, D. Coit. *Surgery, Memorial Sloan-Kettering Cancer Center, Madison, NY.*

Introduction: Positive peritoneal cytology predicts outcome in pancreatic cancer patients. RT-PCR has been proposed as a more sensitive means of detecion of peritoneal micrometastases than conventional cytology and has been shown to increase the yield of detection of micrometastatic disease in pancreatic cancer patients. What is not known is the clinical significance of RT-PCR positivity in the absence of other evidence of peritoneal disease. The purpose of the current study was to determine the outcome RT-PCR positive / cytology negative patients who underwent curative resection. Methods: From February 2006 to May 2008, peritoneal washings were collected prospectively from 112 pancreatic cancer patients undergoing diagnostic laparoscopy at a single institution. All patients were thought to have potentially resectable disease based on clinical staging. Specimens were analyzed by RT-PCR for CEA. Results: Of the 112 patients, 57 (52%) underwent resection with curative intent. Twelve of the 57 patients (21%) who underwent curative resection had peritoneal washings that were positive for CEA by RT-PCR. Those 12 patients had a significantly poorer recurrence free survival versus those who were RT-PCR negative (P<0.05). The 12 RT-PCR positive patients also demonstrated a trend towards decreased disease specific survival versus those that were RT-PCR negative (P=0.08). (Figure) Conclusion: We have previously shown that peritoneal fluid analysis by RT-PCR may increase the yield of detection of peritoneal disease by laparoscopic staging by 28% in pancreatic cancer patients. We have now followed those patients who underwent curative resection with RT-PCR positivity as their only evidence of peritoneal metastasis after staging laparoscopy. RT-PCR positivity in these patients is clinically significant. RT-PCR for CEA is a sensitive and specific method of detection of peritoneal micrometastases from pancreatic cancer and may identify a subgroup of patients with otherwise negative findings at staging laparoscopy who will experience early recurrence and death after curative resection.



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Totally laparoscopic gastric resection with extended lymphadenectomy for adenocarcinoma of the stomach E.A. Guzman,[1]* A. Pigazzi,[1] B. Lee,[2] J. Kim,[1] J.D. Ellenhorn.[1] *1. City of Hope, Duarte, CA; 2. St. Lukes Roosevelt Hospital Center, New York, NY.*

BACKGROUND: Laparoscopic gastric resection is being evaluated in North America as an option for the surgical treatment of gastric cancer. Our goal was to compare short term postoperative and oncologic outcomes of laparoscopic and open gastrectomy procedures. METHODS: We conducted a retrospective review of patients undergoing gastrectomy for gastric cancer at a single cancer center between November 1999 and May 2008. All patients underwent a trans-abdominal resection with curative intent. A totally laparoscopic technique was employed in 22 patients. In a subset of the laparoscopic resections, extended lymphadenectomy was performed with the use of the DaVinci robot. RESULTS: A total of 67 patients underwent gastric resection including 22 laparoscopic and 45 open resections. The laparoscopic and open groups were similar in age, sex, BMI, T stage and overall stage. Both groups were similar with respect to type of gastrectomy (total/partial), type of lymphadenectomy (D1/D2) and resection status (R0/R1). All but one patient had negative resection margins. An extended lymphadenectomy was performed in 50 patients including 15 laparoscopic and 35 open. There was no difference in the mean number of lymph nodes retrieved between laparoscopic and open groups (26 ± 8 vs. 26 ± 14, p=0.91). In D2 lymphadenectomy cases, there was no difference in lymph node counts between laparoscopic and open procedures (28 ± 9 vs. 31 ± 13, p=0.46). Laparoscopic procedures were associated with an increased mean operative time (416 vs. 300 minutes, p<0.0001), but decreased blood loss (279 vs. 534 milliliters, p= 0.03). Median length of stay was significantly lower in the laparoscopic group (7 vs. 10 days, p=0.002). CONCLUSION: Totally laparoscopic gastric resection is an oncologically safe alternative to open surgery in gastric adenocarcinoma. In this study, the use laparoscopic techniques were associated with an increase in operative time but with lower blood loss and length of stay.

Postoperative outcomes of laparoscopic and open gastrectomies

	Laparoscopic (n = 22)	Open (n = 45)	p value*
Number of lymph nodes, mean (std)	26 (8)	26 (14)	0.91
Surgery time (minutes), mean (std)	416 (76)	300 (76)	<0.0001
Estimated blood loss, mean (std)	279 (233)	534 (492)	0.03
Length of stay (days), median (range)	7 (3 - 32)	10 (3 - 67)	0.002♦
% Weight loss at 1 month, mean (std)	6 (6)	7 (4)	0.30
Mortality, N (%)	0 (0)	1 (2)	0.48♧
Complications, N (%)	8 (36)	21 (47)	0.59♧

Std, Standard deviation; N, Number; %, Percentage of patients; *, Student's T test; , Mann-Whitney test; , Chi square statistics.

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Long Term Survival Results of Surgery Alone verses Surgery plus 5-Fluorouracil and Leucovorin for Stage II and Stage III Colon Cancer: Pooled Analysis of NSABP adjuvant trials C-01 through C-05 N.W. Wilkinson,[1]* G. Yothers,[2] S.H. Lopa,[2] J. Costantino,[2] N. Petrelli,[3] N. Wolmark.[2] *1. Surgical Oncology, University of Iowa, Iowa City, IA; 2. National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA; 3. Helen F Graham Cancer Center Newark, Newark, DE.*

The objective of this study was to conduct a pooled analysis of NSABP colon cancer adjuvant trials involving surgery alone and surgery plus 5-Fluorouracil and Leucovorin (5-FU/LV) to compare survival and establish a baseline from which to evaluate future studies. Methods: All patients enrolled in NSABP adjuvant trials C-01 to C-05 with Stage II and III disease who were treated with surgery alone or with surgery plus 5-FU/LV were examined for overall survival (OS), disease free survival (DFS), and recurrence free interval (RFI). Kaplan-Meier estimates were adjusted by the method of Xie and Lui for imbalance of covariates. Multivariable Cox regression analysis was used to compare groups controlling for stage, age, gender, and race. Results: Overall, there were 2,966 eligible patients: 693 (23%) surgery alone and 2,273 (77%) surgery plus 5-FU/LV; 1,255 (42%) Stage II and 1,711 (58%) Stage III. Age ≥ 60 years (HR=1.36, p<0.0001), male gender (HR=1.18, p=0.0026), and stage III disease (HR=1.83, p< 0.0001) were associated with worse survival. At five years, the surgery alone OS was 62% (CI= 0.602- 0.638) and surgery plus 5-FU/LV OS was 76% (CI= 0.743- 0.774). For the entire cohort, treatment with 5-FU/LV was associated with improved outcome compared to surgery alone: OS (HR=0.63, p<0.0001), DFS (HR=0.67, p<0.0001) and RFI (HR=0.65, p<0.0001). Improved OS with adjuvant treatment was seen in both Stage II: HR=0.59 (95% CI=0.48-0.72), and Stage III disease HR=0.66 (95% CI=0.56-0.77). Conclusions: This analysis provides the long term survival outcome of Stage II & III colon cancer examining the primary treatment modalities utilized prior to current regimens. This analysis confirms that treatment of colon cancer patients with 5-FU/LV following surgery provides a substantial benefit over surgery alone for both Stage II and III disease. These results can be used to provide anticipated survival outcomes from which to compare modern adjuvant trials.

Kaplan-Meier estimate of Overall Survival

Time (Years)	Stage II Overall Survival		Stage III Overall Survival	
	Surgery (95% CI)	Surgery + 5-FU/LV (95% CI)	Surgery (95% CI)	Surgery + 5-FU/LV (95% CI)
5	0.768 (0.743, 0.792)	0.869 (0.849, 0.887)	0.515 (0.493, 0.538)	0.678 (0.655, 0.7)
10	0.606 (0.578, 0.633)	0.759 (0.734, 0.783)	0.396 (0.374, 0.418)	0.556 (0.532, 0.58)
15	0.485 (0.453, 0.517)	0.605 (0.568, 0.642)	0.357 (0.334, 0.38)	0.481 (0.455, 0.507)

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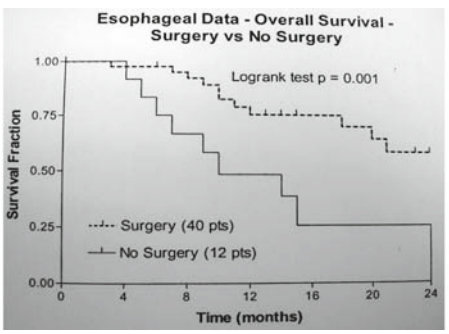
Cetuximab Based Neoadjuvant Chemo Radiation Appears To Facilitate Surgical Resection In Patients With Locally Advanced Esophageal And Gastric Cancer H.J. Wanebo,[1]* H. Safran,[2] M. Suntharalingam,[2] T. Ng,[2] T. Dipetrillo,[2] J. Belliveau,[2] M. Krasna,[3] T. Kennedy.[2] *1. Surgical Oncology, Landmark Medical Center, Woonsocket, RI; 2. Brown University Oncology Group, Providence, RI; 3. University of Maryland, School of Medicine, Baltimore, MD.*

Introduction: Cetuximab, an anti EGFR monoclonal antibody has been shown to augment survival when combined with chemotherapy and/or radiation in cancers of the head and neck and colon. Background: We have conducted a phase II trial of cetuximab based chemo radiation for pts with locally advanced carcinoma of esophagus and stomach with focus on tumor regression, resectability and disease free outcome. Methods: Pts with locally advanced esophageal (55) and gastric cancer (5) (adenoCa-56, squamous Ca-4), (T2-4, N1-3, M0) were enrolled into an IRB approved protocol after endoscopic and radiologic staging. Pts received cetuximab 400mg/M2 week 1, then 250mg/M2 / week for 5 weeks, Paclitaxel 50mg/M2 /week and carboplatin AUC = 2, given weekly for 6 weeks with concurrent 50.4 Gy. Results: Fifty four evaluable patients (47M/7F, median age 58 years completed neoadjuvant therapy: 42 had surgery, 12 had restaging endoscopy only (3 were borderline operable and 9 declined surgery). Major toxicities were gr 3/4 esophageal mucositis- 10 pts –(20%), gr 3/4 dehydration 5pt, and drug hypersensitivity 2 pts. A complete endoscopic response was shown in 28 of 42 (67%) surgical pts and in 10 of 12 having endoscopy only. Major resections included Ivor Lewis (thoracoabdominal +/-cervical reconstruction (28 pts), transhiatal resection (12 pts) and gastrectomy 2 pts. There were 2 post operative deaths. Ten pts (20%) had path CR, and 10 pts (20%) had a near CR (microscopic residual). Short term outcome: overall survival at 2 yrs was 60% with surgery, vs 25% endoscopic evaluation only (p<0001). In surgery group 56% were NED, 35% were DOD and 7% were LWD, at 13 mo median follow up (3-38 mos). CONCLUSION: Cetuximab based neoadjuvant chemo radiation is tolerable, is associated with significant downstaging facilitating surgical resection, and may enhance survival in pts with locally advanced esophageal and gastric cancer.



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A Prospective Study of the False Positive Diagnosis for Micrometastic Cells in the Sentinel Lymph Nodes in Colorectal Cancers

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Introduction: Sentinel lymph node(SLN) mapping(M) of colorectal(CR) cancer(Ca), using multilevel sections(MLS)and cytokeratin immunostaining(IHC)of SLNs, upstages 15-20% of patients(Pts). Occasional identification of benign epithelial cells(BEC) mimicking as micrometastatic disease in the SLNs has been reported in breast Ca. Such BEC has also been reported in benign CR tumors and considered as IHC positive micrometastatic cells. To prove presence or absence of such a phenomenon, a prospective study was undertaken in patients(pts) with CR tumors undergoing SLNM. **Methods:** A total of 314 consecutive pts between April 1996 and Aug 2008 were included in an ongoing prospective study. All pts underwent SLNM with 1% lymphazurin or 1% methylene blue. Ninety out of the 314 pts underwent a second SLNM of normal bowel at least 20 cm from the primary tumor. Within 10 minutes of injection, first 2-4 blue lymph nodes near the primary tumor were marked as SLNs, and those near the second injection site were marked as Non-tumor(NT)SLNs. All true SLNs and NT-SLNs underwent MLS(4 for H&E and 1 for IHC). The remaining specimen was examined by standard methods. **Results:** Of the 314 pts, 284 had invasive CRC and 30 had benign disease. Of these 284 pts, SLNM was successful in 96.5% of pts with a total of 728 SLNs. Thirty one pts(11.3%) had 38 SLNs +ve for micrometastasis(0.2-2 mm) identified by H&E while 15 pts(5.5%) had 19 SLNs +ve for micrometastasis identified by IHC. SLNM was successful in 100% of the 30 pts with benign disease with no BEC identified in any of the 88 SLNs. Of the 90 pts undergoing second SLNM, the success rate was 77.8%(70/90) with 102 NT-SLNs; none had identifiable BEC. Thus, in summary, for 100 total pts with successful SLNM either away from the main tumor or with benign pathology, BEC were absent in 190 SLNs, as compared to 57 positive SLNs in 46(16.8%) out of the 284 pts with invasive disease(p = <0.0001) (table1) **Conclusion:** Our Study confirms SLNM in CR tumors does not induce false positive SLNs secondary to BEC. For CRCa pts, micrometastatic disease found in SLNs is true node +ve disease.

Table 1: Sentinel lymph node mapping in invasive colorectal cancer versus benign pathology and non-tumor SLNM

		SLNM in invasive cancer	SLNM in pts with either benign pathology or non tumor site	p- value
Total number of pts		284	120	
Success rate		274(96.5%)	100(83.3%)	<0.0001†
Site	Colon	220(80.3%)	86(86%)	0.2‡
	Rectal	54(19.7%)	14(14%)	0.2‡
Number of pts with micromets	H&E	31	0	
	IHC	15	0	
	Total	46 (16.8%)	0	<0.0001†
Number of SLNs		728	190	
Number of +ve SLNs for micomets	H&E	38	0	
	IHC	19	0	
	Total	57 (7.8%)	0	<0.0001†

* SLNM=Sentinel Lymph Node Mapping, SLNs=Sentinel Lymph Nodes, H&E=Hematoxylin and Eosin, IHC=Imunohistochemistry.using Chi-Square analysis, using fisher's exact test

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Validation of POSSUM as a Measure of Postoperative Morbidity Following Pancreatic Surgery

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Introduction: The Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) has accurately predicted postoperative morbidity for major abdominal surgery. We sought to evaluate the accuracy of the model in predicting morbidity after pancreatic resections. Methods: Between September 2002 and December 2007, data was prospectively collected on 171 consecutive pancreatic resections. The POSSUM score was calculated retrospectively for each patient using 12 physiologic (age, cadiac and respiratory history, ECG, BP, HR, GCS, Sodium, potassium, BUN, WBC, hemoglobin) and 6 operative(severity, blood loss, multiple procedures, peritoneal soiling, malignacy, and timing of surgery) variables. Each patient was then categorized into one of five groups based on the probability of developing complications. The expected, observed, and the observed to expected morbidity ratio were calculated. Results: The entire cohort consisted of 171 patients with 102 undergoing pancreaticoduodenectomy (PD), 32 distal pancreatectomy (DP), and 37 total pancreatectomy (TP). Patients in all three groups were statistically similar with regards to age and comorbidities. Average blood loss was 1054 ml for TP vs. 632 for PD vs. 583 for DP (p=0.0022). As seen in the table, the observed to expected morbidity within the entire cohort was 0.98. The O/E ratio was closest to 1 in the <20% and 20-40% groups. Evaluation of postoperative complications indicates increasing TPN administration (10% in <20% vs 75% in >80% group;p=0.0002), transfusion requirements (18% in <20% vs 63% in >80% group;p=0.0002), and re-operation (0% in <20% vs 50% in >80% group;p<0.0001)to best correlate with the POSSUM score. As well, patients with increased morbidity risk had longer hospitalizations (10.6 days in <20% vs. 27.9 days in >80% groups;p=0.0004) and decreased chance of being discharged to home directly (p=0.0055). Conclusion: POSSUM is a valid scoring system for the assessment of postoperative morbidity in pancreatic resections. Using this scoring system, we will be able to accurately provide patients and families with a plausible prediction for the perioperative course.

Expected vs. Observed Morbidity

POSSUM Score	Patients (no.)	Predictive Risk (%)	Expected Morbidity (no. of patients)	Observed Morbidity (no. of patients)	O/E Ratio
<20%	71	13.00	9	9	1
20-40%	54	29.40	16	17	1.06
40-60%	25	49.62	12	10	0.83
60-80%	13	67.89	9	8	0.89
>80%	8	83.72	7	8	1.14
Overall	171	31.01	53	52	0.98

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Combination Intraperitoneal Chemotherapy is Superior to Mitomycin or Oxaliplatin for Colorectal Carcinomatosis In Vivo

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Introduction: Heated Intraperitoneal Chemotherapy (HIPEC) after cytoreduction has been well documented to improve survival in patients with colorectal carcinomatosis confined to the peritoneal surface. Most protocols utilize a single agent (mitomycin C or oxaliplatin) given IP. The purpose of this study is to determine if combination intraperitoneal chemotherapy is superior to a single agent and if multidose therapy is better than a single dose application. **Methods:** Female Nu/Nu mice (Charles River) were injected IP with 10^6 HT-29 human colorectal cancer cells known to produce peritoneal-only metastasis. Once IP tumor burden was established, animals were treated IP (5 mice per treatment arm)with either a single dose of drug, control (saline) or drug combination or repeated doses for up to 3 weeks. Primary endpoint was overall survival. **Results:** All study arms are described in Table below. Control animals died by 77 days (mean 60±5d). All single dose, single agent therapies were not statistically better than controls for survival. IP irinotecan with IV 5-FU and Leucovorin (FOLFIRI)had one animal survive 87 days but mean was 59 days and OS was not significant from control. Mitomycin C(3.25 mg/kg)+Irinotecan(20 mg/kg)+panitumumab(0.2mg/kg) for 3 weeks IP had 100% survival (p<0.0001 against controls) at 120 days post treatment without obvious toxicity. Mitomycin C + Irinotecan (same doses for 3 wks IP) had 80% survival at 120days(p<0.001). Irinotecan + Panitumumab (same doses for 3 wks IP) had 40% survival at 120 days(p<0.01). Mitomycin + Panitumumab (same doses x 3 wks) had a 20% survival at 120 days (p<0.01). Single agents with the best survival were irinotecan (20mg/kg weekly x 3 wks)with a median survival of 108 days (p<0.01) mitomycin C (3.25 mg/kg weekly x 3 wks) with a median survival of 95 days (p<0.01). **Conclusions:** Combination IP therapy with mitomycin C, panitumumab and irinotecan was superior to all other agents tested alone or in combination. Multiple drug dosing over 3 weeks resulted in longer survival compared to a single dose. This data warrants further combination analysis and supports consideration for a phase I application.

Comparison of IP Chemotherapy Reigimens for Surivial

DRUG(S)	DOSE(S)	NUMBER OF DOSES	OVERALL SURVIVAL (DAYS)	MEDIAN SURVIVAL (DAYS)	p value vs. controls
CONTROL (saline)	100 uL IP	daily x 3 wks	77	61	n/a
Mitomycin C(MitoC)	3.25 mg/kg	single dose	72	59	NS
MitoC	3.25 mg/kg	1/week x 3 wks	107	95	<0.01
Oxaliplatin	10 mg/kg	single dose	75	64	NS
Oxaliplatin	10 mg/kg	1/week x 3 wks	79	70	NS
Irinotecan	20 mg/kg	daily 5 days/wk x 3 wks	113	108	<0.01
Nanotax	24 mg/kg	1/week x 3 wks	77	62	NS
Panitumumab	0.2 mg/kg	1/week x 3 wks	80	62	NS
Panitumumab	0.2 mg/kg	3x/week x 3 wks	112	64	<0.05
Cetuximab	1 mg	3x/week x 3 wks	72	70	NS
Erlotinib	50 mg/kg	daily 5 days/wk x 3 wks	87	63	NS
MitoC + Panitumumab	3.25 mg/kg + 0.2 mg/kg	(M) 1/week x 3 wks + (P)3x/wk x 3 wks	>120	108	<0.01
MitoC + Irinotecan	3.25 mg/kg + 20 mg/kg	(M) 1/week x 3 wks + (I)daily 5 d/wk x 3 wks	>120	>120	<0.001
5FU + Leucovorin + Irinotecan	60 mg/kg IV+20mg/kg IV+80mg/kg IP	all once/wk x 3 wks	87	59	NS
Irinotecan + Panitumumab	20 mg/kg + 0.2 mg/kg	(I)daily 5 d/wk x 3 wks + (P)3x/wk x 3 wks	>120	115	<0.01
MitoC + Irinotecan + Panitumumab	3.25 mg/kg + 20 mg/kg + 0.2 mg/kg	(M) 1/week x 3 wks +(I)daily 5 d/wk x 3 wks + (P)3x/wk x 3 wks	>120	>120	<0.0001

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A prospective, multi-institutional study of adjuvant radiation therapy after resection of malignant phyllodes tumors R.J. Barth,[1]* W. Wells,[1] B. Cole,[2] S. Mitchell.[1] *1. Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH; 2. University of Vermont, Burlington, VT.*

Background: Malignant phyllodes tumors are an unusual neoplasm, with an incidence of approximately 500 cases per year in the US. It is uncertain whether radiation therapy after resection of malignant phyllodes tumors is beneficial. Methods: We prospectively enrolled 46 patients who had been treated with a margin negative breast conserving resection of a malignant phyllodes tumor to adjuvant radiation therapy. The primary endpoint was local recurrence. For comparison, the literature was searched to determine the incidence of local recurrence after margin negative resection of malignant phyllodes tumors. Results: Forty six patients were prospectively treated between 1/98 and 7/07 at 30 different institutions with margin negative resection and adjuvant radiation therapy. The mean patient age was 49 years (18-76). The mean tumor diameter was 3.7 cm (1-11 cm). Eighteen patients had a negative margin on the first excision. The median size of the closest margin was 0.35 cm (range <0.1 - 2 cm). Twenty eight patients underwent a re-excision because of positive margins in the initial resection. None of the 46 patients developed a local recurrence with a median follow-up of 48 months (range 5-121 months). The local recurrence rate was zero (95% CI 0 - 8%). Two patients died of metastatic phyllodes tumor. In the literature search thirteen studies were identified which described 174 patients with malignant phyllodes tumors treated with margin negative breast conserving resection alone. Thirty seven (21%) experienced a local recurrence. Discussion: Margin negative resection of malignant phyllodes tumors is associated with a substantial risk of local recurrence. In the first prospective study ever reported on patients with phyllodes tumors we have demonstrated that margin negative resection combined with adjuvant radiation therapy is very effective therapy for local tumor control. The local recurrence rate after margin negative resection plus adjuvant radiation therapy was significantly less than that observed when historical controls were treated with margin negative resection alone. (ClinicalTrials.gov number NCT00003404.)

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Contralateral prophylactic mastectomy for unilateral breast cancer: An increasing trend N.B. Jones,[1]* L. Kotur,[2] J. Wilson,[2] J. Stephens,[1] W.B. Farrar,[2] D.M. Agnese.[2] *1. Surgery, The Ohio State University, Columbus, OH; 2. The James Cancer Hospital, Columbus, OH.*

The options for management of women with unilateral breast cancer include breast conservation or mastectomy. Typically, contralateral prophylactic mastectomy (CPM) is entertained in the setting of high risk, as determined by personal or family history. An increasing trend in the use of CPM has been observed nationally. The purpose of this study was to determine whether a similar trend existed in our patient population and to identify differences between the groups that chose unilateral mastectomy (UM) alone or with CPM. A prospective breast cancer database established in 1998 was retrospectively reviewed. Variables evaluated included age, histologic grade, stage, education level, family history, and utilization of immediate reconstruction. Statistical analysis was performed using Fisher's Exact Test, Chisquare Test, and Student's t-test. Between 1998 and 2007, 1,639 women who selected UM and 201 who had both UM and CPM for the management of their unilateral breast cancer were identified. An increasing trend in the utilization of CPM was observed over this 10 year period (6.5% in 1999 vs. 16.1% in 2007). The CPM group was significantly younger than the UM group (mean age 47.8 vs. 55.1, p<0.001). There was no difference in histologic grade between the two groups; however, an increasing trend toward CPM with lower stages (stages 0-1) was observed (p=NS). A larger proportion of more highly educated women (some college to graduate or professional school) chose to have CPM than less educated women (14.8% vs. 7.7%, p<0.001). More women with a positive family history elected to undergo CPM than those without family history of cancer (14.3% vs. 8%, p<0.001). Utililization of reconstruction was similar between the two groups, (6.0% of the CPM group vs. 6.65% of the UM group, p=NS). Our experience parallels the national trend of increasing use of CPM in women diagnosed with unilateral breast cancer. Women who chose to have CPM were younger, more highly educated, and more likely to have a family history of cancer. They also tended to have lower stage disease, although this was not statistically significant. Additional research is necessary to evaluate these trends.

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The prognostic significance of tumor surgery in patients with primary metastatic breast cancer J. Ruiterkamp,[1]* A.C. Voogd,[2] T. Smilde,[1] K. Bosscha,[1] M.F. Ernst.[1] *1. Surgery, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands; 2. University Hospital Maastricht, Maastricht, Netherlands.*

Purpose In the Netherlands approximately one out of nine women are diagnosed with breast cancer annually. 3-10 % of them have metastatic disease at initial presentation. Because metastatic breast cancer is considered to be an incurable disease, it is treated palliatively. Local treatment of the primary tumor is only recommended if the primary tumor is symptomatic. In order to analyse whether local surgery of the breast tumor affects the survival of patients with primary metastatic breast cancer, a retrospective study was conducted. Methods In the period 1975 till 2002 approximately 20.000 patients with breast cancer were diagnosed in the South of the Netherlands. Metastatic disease at initial presentation was detected in 5 %. The use of local surgery of the breast tumor was examined in the latter group. The primary goal was to analyze the effect on survival. Multivariate analyses were conducted to compare overall survival between operated and non-operated patients. Adjustments were made for age, TNM-classification, localisation and number of metastases and co-morbidity. Results Of the 728 patients identified, 288 underwent surgical excision of the primary tumor. Median survival in patients who were treated with local surgery was 2,55 years, compared with 1,17 years in patients who did not receive surgical treatment (p<0,0001). Significant independent prognostic covariates for a better prognosis are surgery, age, number of metastatic sites and systemic therapy. After controlling for potential confounding, patients who are treated surgically, have a lower mortality risk with a hazard ratio (HR) of 0,69. Patients with multiple metastases and co-morbidity have a reduced effect of the surgical treatment, though the effect is still significant. Conclusions Local surgery of the tumor in patients with primary metastatic breast cancer is associated with a significant reduction of the mortality risk. The association is independent of age and co-morbidity, but appears to be stronger in patients with an isolated metastatic site. Further research is necessary and therefore a randomized controlled trial should be designed in order to rule out unsuspected confounding.

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African American (AA) Women with DCIS are Equally Likely to Participate and Develop Immune Response to Experimental Neoadjuvant HER-2/neu Targeted Vaccine A. Sharma,[1]* R. Mick,[2] U. Koldovsky,[1] S. Xu,[1] R.E. Roses,[1] H. Nisenbaum,[3] P.J. Zhang,[4] B.J. Czerniecki.[1] *1. University of Pennsylvania, Department of Surgery, Philadelphia, PA; 2. University of Pennsylvania, Department of Biostatistics and Epidemiology, Philadelphia, PA; 3. University of Pennsylvania, Department of Radiology, Philadelphia, PA; 4. University of Pennsylvania, Department of Pathology and Laboratory Medicine, Philadelphia, PA.*

INTRODUCTION Multiple studies have analyzed racial disparities in invasive breast cancer but few, if any, in ductal carcinoma in situ (DCIS). In this

study, we analyze racial disparities among a cohort of DCIS patients that participated in an experimental neoadjuvant HER-2/neu (HER-2) targeted vaccine trial. METHODS Data regarding demographic, pathologic and immune response was reviewed from our DCIS vaccine trial database of 106 patients. Thirty patients were initially eligible and consented to participate in this clinical trial. Patients received 4 weekly vaccines of autologous type I dendritic cells pulsed with MHC class I and class II HER-2 derived peptides. HER-2 status was considered positive if the immunohistochemistry score was 2+ on 10% or greater of the DCIS. Response to vaccination was assessed by CD4/CD8 measurements in peripheral blood and sentinel nodes using in-vitro immunomonitoring tests. Association between race and participation, post-vaccination HER-2 status and response was performed utilizing Fisher's exact test. RESULTS Substantially lower rates of HER-2 positivity were found in AA women. 33% of AA women with DCIS were HER-2 positive compared to 55% of Caucasian (C) women, p=0.05. AA women were also equally likely to participate in the trial (p= 0.46). Both AA and C women tolerated vaccination with minimal grade I and II toxicities. Most importantly there was no statistical difference between race and post vaccination immune response in peripheral blood or sentinel node as well as post-vaccination HER-2 status in any residual DCIS (p= 0.46-1.00). Interestingly, all AA women developed an immune response post-vaccination. CONCLUSION These results suggest that if properly informed and offered the opportunity, AA women are likely to participate in immune based therapies for breast cancer and are equally likely to develop an immune response against HER-2. The intriguing observation that AA women are less likely to over-express HER-2 in DCIS compared to C women is worthy of additional investigation. This study is one the first to address immune response to a HER-2 vaccine in AA women.

Data Table for Neoadjuvant HER-2/Neu Targeted Vaccine Trial

	AFRICAN AMERICAN				CAUCASIAN				
	Patients	Events	Rate	90% CI	Patients	Events	Rate	90% CI	Fisher's Exact P-Value
HER-2/neu Status	30	10	33.3%	19.3-50.0%	65	36	55.4%	44.5-65.9%	0.05
Participation	10	8	80.0%	49.3-96.3%	36	22	61.1%	46.0-74.7%	0.46
HER-2/neu Response	6	3	50.0%	15.3-84.7%	21	9	42.9%	24.5-62.8%	1.00
CD4 Response	6	6	100%	68.1-100%	20	17	85.0%	65.6-95.8%	0.56
CD8 Response	2	2	100%	31.6-100%	10	8	80.0%	49.3-96.3%	1.00
Sentinel Node Response	5	5	100%	63.1-100%	16	13	81.3%	58.3-94.7%	0.55

CI= Confidence Interval; Response = post vaccination

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External Beam Radiation Therapy significantly reduces the risk of developing axillary recurrences after negative SLNB; a systematic review B.J. Van Wely,[1]* T.J. Aufenacker,[1] M. Schouten,[2] D.A. Schinagl,[2] L.J. Strobbe.[1] *1. Canisius Wilhelmina Hospital, Nijmegen, Netherlands; 2. Radboud University Medical Centre, Nijmegen, Netherlands.*

Introduction Axillary recurrences after negative Sentinel Lymphnode Biopsy (SLNB) in patients with invasive breast carcinoma remains a concern. For this study a prospective database was used to identify prognostic factors of importance in developping an axillary recurrence after negative SLNB; the vast majority of axillary recurrences occurred in patients initially treated without External Beam Radiation Therapy (EBRT) to the breast (i.e. mastectomy). This finding initiated a systematic review to test the hypothesis that EBRT to the breast, given as part of initial treatment, reduces the risk of developing axillary recurrences after negative SLNB. Patients and methods A literature search was performed in PubMed, Cochrane Library and the spanish-language database LILACS with the search terms "Breast Cancer", "SLNB", "recurrence", "axillary" and "related articles", to identify articles publishing data regarding follow up of Sentinel Lymphnode (SLN) negative patients. In respect of the aim of this study, the specific initial treatment was of most importance. Therefore reports and articles lacking information on initial treatment information were excluded. When the initial treatment information was not available an attempt was made to contact the author trying to collect the missing information. Chi square analysis is performed on the data. Results 35 articles were found, and 23 were eligible for review. A total of 10.576 SLN-negative patients were identified with median follow up ranging from 21-76 months. 8.207 patients recieved EBRT to the breast as part of their initial treatment, 2369 did not. Sixty-two patients with an axillary recurrence were identified. In 27 out of 62 patients, EBRT was part of the initial treatment. Chi square analysis resulted in a significant difference (p<0,0001). Conclusion This systematic review demonstrates a significant reduced chance of developing an axillary recurrence, when SLN negative patients are initially treated with EBRT to the breast. This is probably caused by irradiation to the caudal part of the axilla which could be enough to eradicate micrometastasis not detected by SLNB.

Radiation therapy and axillary recurrence

	No-RT	RT	total
SLN-negative patients	2369	8207	10576
Recurrences	35	27	62
percentage	1.48%	0.03%	**p<0,0001**

No-RT= did not recieve radiation therapy, RT= did recieve radiation therapy

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Management of Sentinel Node Micrometastases in Breast Cancer: Lack of Adherence to Established Guidelines N. Wasif,* X. Ye, A.E. Giuliano. *John Wayne Cancer Institute, Santa Monica, CA.*

Introduction: Regional management choices for sentinel node (SN) micrometastasis (N1mic) in breast cancer include observation, axillary dissection (ALND), chemotherapy and/or axillary radiation. We hypothesized that treatment decisions for SN MM vary by medical specialty. Methods: A questionnaire was emailed to 2511 active members of the American Society of Clinical Oncology, who specialize in breast cancer and are board certified in radiation oncology, surgery, or medical oncology. Questions covered treatment of SN micrometastases (MM). Survey responses were analyzed using the Kruskal-Wallis and Fisher's exact test. Results: Of 612 questionnaires viewed by recipients, 537 (88%) were completed by 382 medical oncologists, 100 surgeons and 55 radiation oncologists. The majority (98.5%) regarded N1mic as clinically significant. Isolated tumor cells (N0i+) in the SN were considered unimportant by 53% of respondents (no significant difference among groups) and of undetermined importance by 28%. Similarly, RT-PCR positivity of the SN (N0mol+) was considered unimportant by 57% (no significant difference among groups) and of undetermined importance by 32%. Most respondents in each specialty (89% overall) would consider adjuvant chemotherapy for primary tumors <1cm if N1mic disease were present. Primary tumor size, patient age, MM size, lymphovascular invasion (LVI), ER/PR status, HER-2 neu status and gene expression profile (Oncotype DX) would influence this decision. ALND for N1mic was recommended by only 23% of surgeons, 23% of medical oncologists, and 15% of radiation oncologists (no significant intergroup difference). Radiation oncologists (76%) were more likely than medical oncologists (57%) or surgeons (47%) to consider axillary radiation instead of axillary dissection for N1mic (p=0.0021). Conclusion: Guidelines recommending ALND for all N1mic disease are not being followed by a majority of oncology specialists surveyed.

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Factors Associated with Optimal Cosmetic Results in Patients Treated With Accelerated Partial Breast Irradiation (APBI) by the American Society of Breast Surgeons (ASBrS) MammoSite® Breast Brachytherapy Registry Trial S. Goyal,[1]* F. Vicini,[2] P.D. Beitsch,[3] M. Lyden,[4] B.G. Haffty.[1] *1. The Cancer Institute of New Jersey - UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ; 2. William Beaumont Hospital, Royal Oak, MI; 3. Dallas Breast Center, Dallas, TX; 4. BioStat International Inc, Tampa, FL.*

Purpose: To evaluate factors associated with optimal cosmetic results for early-stage breast cancer patients enrolled on the American Society of Breast Surgeons (ASBrS) MammoSite® Breast Brachytherapy registry trial. Materials and Methods: 1440 patients (1449 cases) at 97 institutions with early-stage breast cancer undergoing breast conserving therapy were treated with the MammoSite® RTS brachytherapy to deliver adjuvant APBI (34 Gy in 3.4 Gy fractions). Cosmetic outcome was evaluated at each follow-up visit and dichotomized as excellent/good or fair/poor. Median follow-up for surviving patients was 43.0 months (range, 0-73.0). Results: The percentage of patients with good/excellent cosmetic results at 12, 24, 36 and 48 months were as follows: 94.5% (n=946), 93.7% (n=769), 93% (n=652), and 89.9% (n=382). Four year absolute rates of good/excellent cosmesis are as follows: breast-related wound infection (BWI) (86.5%) vs. no BWI (91%), chemotherapy (88%) vs.

no chemotherapy (91%), and A/B cup (83%) vs. C/D cup (93%). Using multiple regression analysis, factors predictive of worse cosmetic outcome included smaller breast size (OR 0.65, CI: 0.46-0.93), seroma formation (OR 0.59, CI: 0.41-0.83), smaller skin spacing (OR 1.09, CI: 1.05-1.14), use of chemotherapy (OR 0.45, CI: 0.29-0.71) and BWI (OR 0.38, CI: 0.25-0.58). Use of chemotherapy in patients with BWI increased the risk of a fair/poor outcome 10-fold compared chemotherapy patients without BWI; in non-chemotherapy patients, BWI increased this risk 2-fold (p=0.02). Age (OR 0.99, CI: 0.98-1.0), location of tumor (OR 1.34, CI 0.78-2.3), and balloon fill (OR 0.89, CI: 0.63-1.26) were found not to be associated with cosmetic outcome. Conclusion: APBI delivered by Mammosite® brachytherapy lead to good/excellent cosmesis in 90% of patients with 4 year follow-up. While these variables may be associated with a poorer cosmetic outcome in a minority of patients the vast majority of these patients have a good/excellent cosmetic result.

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Metastatic-Site Specific Differential Protein Expression and Growth Control in Breast Cancer Through MicroRNAs J.B. Patel,[1]* P. Nakshatri,[1] W. Guohua,[1] M.J. Thomson,[2] S. Hammond,[2] Y. Liu,[1] H. Nakshatri.[1] *1. Surgery, Indiana University School of Medicine, Indianapolis, IN; 2. University of North Carolina, Chapell-Hill, NC.*

(a) Gene expression differences between primary and metastatic cancer cells may be regulated differentially at the post-transcriptional level. MicroRNA-mediated inhibition of mRNA stability and translation has emerged as a major regulatory mechanism. The goals of this study are to determine whether metastatic cancer cells express different levels of microRNAs than primary cancer cells and whether this contributes to metastasis site-specific changes in protein expression. (b) Using MD-231 breast cancer cells as a model system, we isolated the following cell lines: primary MD-231 that grows as a tumor in the mammary fat pad of nude mice (TMD-231), lung metastasis (LMD-231), bone metastasis (BMD-231), adrenal gland metastasis (ADMD-231), and brain metastasis (BrMD-231). The expression of 254 microRNAs was measured by microarray techniques. The differential expression of microRNAs between cell lines was further verified by qRT-PCR. Finally, the effects of this differential microRNA expression on their downstream targets were verified by western blotting. (c) 20 microRNAs were upregulated and 7 were downregulated in metastatic cancer cells compared to TMD-231 cells. Specifically, we observed a reduction of the microRNA miR-22 in metastatic cancer cells. The targets of miR-22 include the ErBB3 oncogene and the SIRT1 histone deacetylase. Our studies demonstrated over-expression of ErBB3 and its heterodimerizing partner Her-2 in metastatic cancer cells compared to MD-231 cells. Also, BMD-231 cells showed increased expression of TLR4; while LMD-231 and ADMD-231 cells showed increased expression of Ras compared to both MD-231 and TMD-231 cell lines. This differential expression of TLR4 and Ras in metastatic cancer cells may be linked to downregulation of the microRNA Let-7. Additional studies are underway to identify oncogenic pathways activated in metastatic cancer cells through microRNAs. (d) Metastatic cancer cells may adapt to an organ-specific microenvironment by increasing specific oncogenic signaling proteins through down-regulation of microRNAs. Identifying these pathways may help to manipulate tumor behavior and design more effective therapies.

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Dermatofibrosarcoma protuberans (DFSP): How wide should we resect? J.M. Farma,* S.S. Marzban, M.M. Bui, C.A. Puleo, J.L. Messina, V.K. Sondak, J.S. Zager. *Moffitt Cancer Center, Tampa, FL.*

Introduction: DFSP is a rare dermal tumor with reported local recurrence rates ranging from 0-50%. Controversy exists regarding margin width and excision techniques, with some advocating Mohs surgery and others wide excision (WE) with ≥3cm margins. We reviewed our experience with WE of DFSP using 1-2cm margins and total peripheral margin pathologic evaluation. **Methods:** An IRB approved retrospective review of patients (pts) with DFSP from 1994-2008. Pts had an initial WE using predominately 1-2cm margins with primary closure or delayed reconstruction; further WE was done if possible for any positive margin. Meticulous pathologic analysis with en face sectioning plus immunochemistry when necessary was done on all peripheral margins. We evaluated margin width measured from the visible edge of tumor, number of WE needed for negative margins, reconstruction methods, use of postoperative radiation (RT) and outcomes. **Results:** 85 DFSP pts (M:34, F:51), median age 40 years (range 3-84), were treated by WE. Locations were trunk (47), extremities (25), and head & neck (13). No pt had Mohs surgery. The median number of WE to achieve negative margins was 1 (range 1-3) with a median WE margin of 1.5cm (range 0.5-3cm). Closure techniques included primary closure (64; 75%), skin grafting (21; 24%), and tissue flaps (2; 2%). Four pts had fibrosarcomatous changes, 1 received RT. Five other DFSP pts received RT: 3 head & neck DFSPs with positive margins after multiple WE, and 2 large trunk DFSPs with close negative margins. At a median follow-up of 40 months (range 1-151), 1 pt (1.1%) recurred locally after multiple WE and RT for persistently positive margins. **Conclusions:** Using a standardized surgical approach including meticulous pathologic evaluation of margins, a very low recurrence rate (1.1%) was achieved with relatively narrow margins (median 1.5cm) and avoiding RT in the vast majority of cases, allowing primary closure in 75% of pts. This approach spares the additional morbidity associated with wider resection margins and the additional operative time and open wounds between procedures associated with Mohs surgery. Mohs still plays a role when maximal tissue conservation is needed, such as on the face.

Table 1: Treatment Characteristics of Patients Treated with DFSP

Characteristics	N
Total Patients	85
M:F	34:51
Median Age (years,range)	40 (3-84)
DFSP	81
DFSP with fibrosarcoma	4
Location	
Trunk	47
Extremity	25
Head/Neck	13
Median Number of Excisions	1
Median Margin (cm,range)	1.5 (0.5-3)
Closure Technique Used	
Primary Closure	64 (75%)
Skin Graft Closure	21 (24%)
Complex Flap Closure	1 (1.1%)
Recurrence Based on Margins Taken	
0.5-1.0 cm	0
1.0-2.0 cm	1
>2.0 cm	0

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Intratumoral vaccination of oncolytic herpesvirus encoding GM-CSF induces antitumor immunity in stage IIIc and IV melanoma patients H.L. Kaufman,[1]* S. Kim-Schulze,[1] D. Kim,[1] B. Taback,[1] G. DeRaffele,[1] J. Mitcham,[1] H. Goldsweig,[2] R. Coffin.[2] *1. Columbia University, New York, NY; 2. Biovex, Inc., Cambridge, MA.*

Background: An oncolytic herpes simplex virus engineered to replicate selectively in melanoma cells and deliver GM-CSF has been developed for direct intratumoral vaccination. Phase II clinical trials have shown promising therapeutic activity with objective responses (OR) in 25-30% of patients with Stage IIIC and IV melanoma. This study was done to characterize the effect of vaccination on local and distant antitumor immunity. Method: Metastatic melanoma patients with accessible lesions were enrolled in a Phase II clinical trial of OncoVexGM-CSF. A priming dose of 106 pfu vaccine was given by Intratumoral injection followed by 108 pfu every 2 wks up to 16 total doses. Peripheral blood, serum and tumor tissue were collected for analysis of cytotoxic T cell responses, CD4+Foxp3+ T cells (Treg) and soluble factors. Result: 11 patients were treated with OncoVexGM-CSF at our institution and resulted in ORR of 3/11 (27%) by RECIST and an additional two patients were rendered surgical CRs (5/11). Analysis of CD8+ T cells at the tumor site of a CR patient revealed a significant increase in MART-1 specific T cells with a frequency of 8695 cells/1 x 106 cells. Non-target lesion TIL also showed an increase in MART-1 specific T cells. Whereas Treg frequency was generally higher in tumor compared to the circulation (25.37% vs. 9.45%), the frequency in the injected lesion showed a significant decrease compared to uninjected lesions of a CR patient (5.52% vs. 25.06%). Systemic Treg monitoring in non-responding patients showed a persistently higher frequency before and after vaccination. Serum vascular endothelial growth factor (VEGF) levels in patients was elevated compared to normal donors (234.1 vs. 34.85 pg/ml) and higher VEGF levels were found in patients with PD compared to those with ORR

(286.4 vs. 168.8 pg/ml). Conclusions: While previous Phase II data suggested that OncoVexGM-CSF induced clinical responses in 25-30% of patients, we now show that these responses are associated with an increase in local and systemic antigen-specific CD8+ T cells and a decrease CD4+ Tregs and serum VEGF. A randomized Phase III clinical trial is planned.

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Melanoma without Detectable Primary Site with Metastases to Lymph Nodes Z.I. Nowecki, P. Rutkowski,* W. Dziewirski, A. Pienkowski, M. Salamacha, W. Michej, E. Bylina, W. Ruka. *Soft Tissue/Bone Sarcoma and Melanoma, Cancer Center-Institute Warsaw, Warsaw, Poland.*

Introduction. The aim of the study was to analyze of the outcome and pattern of the first recurrences of patients with nodal melanoma metastases (stage III) without detectable primary tumor (UPM – unknown primary site melanoma) as compared to patients after radical therapeutic lymph node dissection (LND) with known primary melanoma (KPM). Methods. We analyzed the data of 449 consecutive patients, who underwent radical LND due to clinically detected (palpable) and pathologically confirmed lymph node metastases in 1994-2006. Median follow-up time from the date of LND was 48 months. Results. In 47 cases (10.5%) therapeutic LND was performed due to UPM (25 male and 22 female; median age: 50 years) nodal metastases: 24 axillar and 23 ilio-inguinal [in 2 cases LND of 2 basins was performed; N1- 12, N2 - 13, N3 – 22 cases]. 5-year overall survival (OS) rate in the UPM group (calculated from the date of LND) was 40% (median 35 months), what was insignificantly better than 5-year OS in the KPM after LND - 32% (median 24 months). OS in the UPM group was influenced by established prognostic factors for AJCC stage III melanoma: the number of metastatic nodes (p=0.004) and the extracapsular extension of metastases (p = 0.05). Analysis of the first relapses (27 cases - 57%) in the UPM group [4 lymph nodes (15%), 5 subcutaneous tissue (18.5%), 5 lung (18.5%), 8 abdominal viscera (30%), 3 bones (11%) and 2 brain (7%)] in comparison to KPM group (299 cases – 74%) demonstrated similar pattern of recurrences. Conclusions: Surgical treatment (LND) performed in all patients with lymph node metastases from occult melanoma should be just as radical as the in case of stage III patients with known primary melanoma location, because the survival rates in UPM group are insignificantly better and affected by same prognostic factors.

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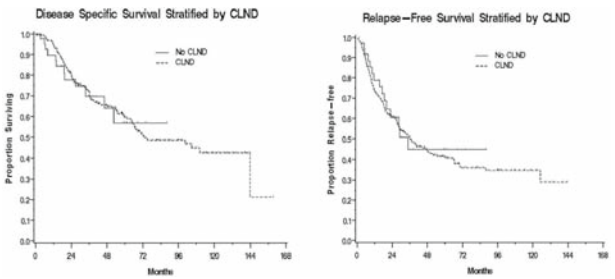
Natural History of Patients With a Positive Sentinel Lymph Node who do not Undergo Completion Lymphadenectomy T. Kingham,* K. Panageas, C.E. Ariyan, K. Busam, M.S. Brady, D.G. Coit. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Completion lymph node dissection (CLND) is recommended for patients with a positive sentinel lymph node (+SLN). Despite this guideline, 50% of patients in the U.S. do not undergo CLND (-CLND). This study was undertaken to describe the natural history of melanoma patients with a + SLN who do not undergo CLND, and to compare that to a contemporary single institution cohort of SLN+ patients who underwent CLND. Methods: A prospective database was utilized to identify all patients with a positive SLN from 1992-2008. Age, primary tumor site, tumor depth, Clark level, tumor ulceration, number of + SLNs, recurrence pattern, reason for not performing a CLND, and current status were evaluated. The Mann-Whitney U test and Kaplan-Meier survival curves were utilized to evaluate the data. Results: 313 patients had +SLNs. 271 (87%) had a CLND and 42 (13%) did not. Median follow-up was 43 months in the +CLND group and 32 months in the -CLND group. Patients in the -CLND group were older than those in the +CLND group with median ages of 70 yrs and 56 yrs, respectively (p<.01). There was a trend towards thicker melanomas in the -CLND group (3.5mm vs. 2.8mm, p<.06). Clark level and tumor ulceration were similar between the groups. The reasons for not performing a CLND included patient refusal (45%), patient and physician decision (33%), metastatic disease found after SLN biopsy (12%), comorbidities (5%) and unknown (5%). There were 146 recurrences (54%) in the +CLND group and 20 (48%) in the -CLND group. There was no difference in pattern of recurrence, with similar nodal basin relapses in the –CLND group and the + CLND group (10% vs 10%, p=NS). Relapse-free survival was similar between the +CLND and -CLND groups (median 34 months and 36 months respectively, fig 1). Median disease-specific survival was also similar, with 73 months for the +CLND group and median not reached for the –CLND group (p=NS). Conclusion: Omitting CLND in melanoma patients with a positive SLN does not necessarily place them at higher risk of recurrence or death. It remains unclear if CLND must be performed in all patients with a positive sentinel lymph node.



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Regional Therapy for Recurrent Metastatic Melanoma Confined to the Extremity: Hyperthermic Isolated Limb Perfusion vs. Isolated Limb Infusion D.S. Reintgen,[1]* S. Pendas,[1] J. Jakub,[2] H. Chan,[1] C. Nobo,[3] C. Puleo,[4] S. Shivers.[5] *1. Surgical Oncology, Lakeland Regional Cancer Center, Lakeland, FL; 2. Gastroenterologic and General Surgery, Mayo Clinic, Rochester, MN; 3. University of South Florida College of Medicine, Tampa, FL; 4. Cutaneous Oncology Program, H. Lee Moffitt Cancer Center, Tampa, FL; 5. Translational Research, Lakeland Regional Cancer Center, Lakeland, FL.*

Introduction: Melanoma patients with recurrent disease confined to an extremity can be offered one of two regional therapies that both give high complete response rates. Isolated limb infusion (ILI) is a newer technique performed with catheters and tourniquets that has less potential morbidity, but decreased efficacy and it does not treat the regional nodal basin. Hyperthermic Isolated Limb Perfusion (HILP) is an open surgical technique that includes removal of the regional nodal basin as part of the surgical procedure. We performed an analysis of the rates of regional nodal disease in patients treated with the HILP procedure to determine the percentage of patients with stage III metastatic disease to the lymph nodes that would have been untreated with the ILI technique. Methods: A retrospective, IRB-approved review of our prospective melanoma database was performed to identify all patients treated with HILP for recurrent melanoma confined to an extremity. All patients had pre-operative physical exams, CT scans and/or PET scans to confirm the presence of isolated disease. All patients underwent a regional node dissection as part of the procedure and all patients were subsequently perfused with melphalan. Results: A total of 233 patients with melanoma underwent a HILP procedure with regional lymph node dissection as is our standard between 3/2002 and 8/2008. There were 105 males and 128 females with a mean age of the population of 64.5 years. Ninety of the 233 patients (39%) had metastatic regional nodal disease documented at the time of the HILP procedure. Conclusion: ILI is a new technique touted as a regional therapy for patients with recurrent melanoma confined to an extremity. Proponents of the procedure state that efficacy is better than what can be achieved with systemic therapy and in comparison to the HILP procedure, has less morbidity. However, our data would suggest that a full 39% of patients may be inadequately treated with the ILI procedure since it does not effectively treat the regional nodal basin.

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Tumor Mitotic Rate Impacts the Incidence of Locoregional and Systemic Recurrence but not SLN Positivity in Patients with Malignant Melanoma S. Carpenter,* R.J. Gray, A. Sekulic, S. Laman, B.A. Pockaj. *Mayo Clinic Arizona, Phoenix, AZ.*

Introduction:Tumor Mitotic Rate (TMR) is a proposed prognostic indicator in cutaneous malignant melanoma. Little is known about the correlation between TMR and sentinel lymph node (SLN) metastases and tumor recurrences. Methods:Retrospective review of a prospectively collected database of patients treated for cutaneous malignant melanoma with surgical resection and SLN biopsy at a single institution over 11 years. Patients with multiple concurrent cutaneous melanomas were excluded. Pearson chi squared analy-

sis was performed to analyze associations between TMR and melanoma recurrences as well as SLN status. Results: 420 patients were treated with wide local excision (WLE) and SLN biopsy for malignant cutaneous melanoma. Mean age was 62 years. 249 (60%) were male. Mean depth was 1.98 mm with T stage classification of T1 in 113 (27%), T2 in 180 (43%), T3 in 86 (21%), and T4 in 34 (8%). 95 patients (26%) had ulcerated lesions. 48 (12%) had positive SLN biopsies. At last follow-up, recurrences included 23 (5.5%) local/in-transit, 19 (4.5%) regional, and 24 (5.7%) distant. TMR (Table 1) was recorded as 0.0-0.99 per mm2 in 102 (24%), 1-4 per mm2 in 134 (32%), 5-10 per mm2 in 73 (17%), > 11 per mm2 in 18 (4%), and was not recorded in 95 (23%),. There was no significant difference in age, sex, thickness, or presence of ulceration between the "not recorded" group and the defined TMR groups. TMR and SLN status were not significantly related (p=0.58), but percent of patients with positive sentinel lymph nodes increased with higher TMR. TMR was predictive of local/in-transit (p=0.02), regional (p=0.001) and systemic (p=0.01) recurrences. The highest TMR category (>11/mm2) was associated with high rates of local/in-transit recurrence (22%), regional recurrence (17%), and distant recurrence (11%).Conclusion:Higher TMR is associated with an increased risk of local/in-transit, regional, and systemic recurrence. This data could be valuable for clinical decision-making and future treatment algorithms. However, due to small sample size, this data must be correlated with larger data sets before statistical reliability can be achieved.

Table 1: TMR Classification, SLN Status, and Recurrence

	Not Recorded N=95	0.0-0.9/mm2 N=102	1-4/mm2 N=134	4-10/mm2 N=73	> 11/mm2 N=18
SLN+	8 (8%)	10 (10%)	15 (12%)	10 (14%)	3 (17%)
Local/Intransit Recurrence N=23	4 (4%)	5 (5%)	6 (4%)	4 (5%)	4 (22%)
Regional Recurrence N=19	3 (3%)	1 (1%)	4 (4%)	9 (12%)	3 (17%)
Systemic Recurrence N=24	7 (7%)	4 (4%)	3 (2%)	8 (11%)	2 (11%)

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Validation study of the S-classification for melanoma in positive sentinel nodes R.J. Younan,[1]* A. Bougrine,[2] K. Watters,[2] M. Bouchereau-Eyegue,[1] A. Loutfi,[2] F. Tremblay,[2] D. Bouffard,[1] A. Belisle,[1] G. Leblanc,[1] E. Nassif,[1] G. Martin,[1] E. Patocskai,[1] S. Meterissian.[2] *1. University of Montreal Health Center (UMHC), Montreal, QC, Canada; 2. McGill University health Center (MUHC), Montreal, QC, Canada.*

Introduction: The standard of care is to perform a complete lymph node dissection (CLND) in melanoma patients with positive sentinel lymph nodes (SLNs). However, only up to 20% of these patients will have metastases in non-SLNs. A German group led by Starz H recently described the S-classification (SI, SII or SIII) to predict the non-SLN status in hope of identifying a subset of patients who can be spared the CLND when the SLN is positive. It is determined by measuring the size of the sub-capsular melanoma deposit within the SLN. We tried to validate the usefulness of this classification. Methods: We performed a retrospective chart review. All melanoma cases between 1996 and 2006 were retrospectively reviewed and 361 patients requiring SLN biopsies were identified. All the pathology slides were reviewed with an emphasis on the S-classification. Results: There were 375 SLN biopsies performed. Eighty-two patients (22.7%) had positive SLNs while 273 patients (75.6%) had negative SLNs. Twenty-two patients were classified as SI, 18 as SII, 35 as SIII, 5 as non-SI and 3 as unknown status. On CLND, only thirteen patients (15.9%) had positive non-SLNs. None of these were classified as SI while 2 patients (11%) were classified as SII and 9 (26%) as SIII. The S-category was found to be a predictor of non-SLN status and this reached statistical significance (p=0.0314). A status different than SI versus an SI status was found to be predictive of non-SLN positivity. On univariate analysis, only an increasing Breslow depth and ulceration were predictive of a non-SI status. The Memorial SU-score could be calculated on only 65 patients. Eight percent of SU-score = 0 patients had positive non-SLNs while 25% of patients with an SU-score = 2 had such findings. Conclusion: Our results suggest that the S-classification is easily feasible and predicts the status of non-SLNs. No patient with an SI status was found to have additional non-SLN positive nodes. A larger scale, prospective trial, should be done to confirm these results and possibly spare patients the morbidity of a universal CLND with a positive SLN.

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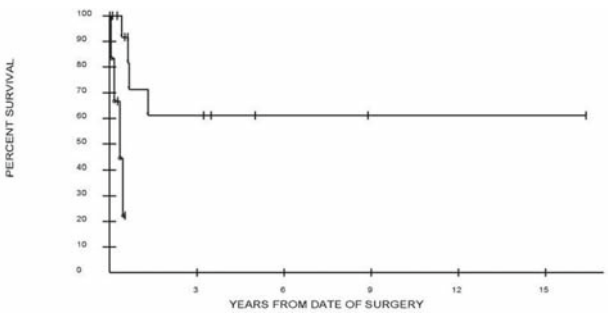
Liver Resection for Metastatic Melanoma with Post-Operative Tumor-Infiltrating Lymphocyte Therapy R.T. Ripley,[1]* J.L. Davis,[1] J.A. Klapper,[1] U. Kammula,[1] R.E. Royal,[1] J.C. Yang,[1] R.M. Sherry,[1] M.S. Hughes,[1] S.K. Libutti,[1] D.E. White,[1] S.M. Steinberg,[2] M.E. Dudley,[1] S.A. Rosenberg,[1] I. Avital.[1] *1. Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; 2. Biostatics and Data Management Section, Office of the Clinical Director, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD.*

Introduction: Metastatic melanoma to the liver (MML) has a median survival (MS) of 4-6 mo. The aim was to evaluate patients who progressed on systemic therapy and underwent liver resection with intent to receive post-operative tumor-infiltrating lymphocytes (TIL). Methods: A retrospective analysis of a prospective database identified patients who underwent liver resections from 1980 - 2008. Clinicopathologic factors were evaluated using univariate and multivariable (Cox Model) analysis. Results: 1849 patients enrolled on immunotherapy protocols; 539 patients had MML; 204 had tumor harvests. 35/204 (17%) patients underwent liver resection for TIL. 3-yr survival of 35 patients was 53% with MS of 3.0 yrs. Lack of extrahepatic disease (EHD) (p=0.026), negative margin (p=0.056), and a single hepatic metastasis (p=0.04) approached significance as predictors of survival. No factors were statistically significant when adjusted for multiple comparisons. Only EHD was independently associated with survival when evaluated in a Cox model. 11/35 (31%) patients underwent complete resection without TIL. 2 patients had post-op gene transfer therapy. For the other 9 patients, 3-yr survival was 80% and MS had not been reached (7–140+mo). 4/9 (44%) recurred with median DFS of 1.2 yrs. 2 patients had resections of recurrences and remained NED. 24/35 (69%) patients who had liver and synchronous EHD underwent liver resections with intent to receive TIL; 2 patients excluded secondary to post-op gene transfer therapy. 3-yr survival of the remaining 22 patients was 51% and MS had not been reached (0.7-197+mo). 15 (63%) patients received post-op TIL and had 3-yr survival of 65% with MS that had not been reached (5–197+mo). 6/15 (40%) patients experienced objective clinical responses; 4 (67%) had not progressed with median follow-up of 55 (42–197+) mo. The MS of 7 patients who did not receive TIL was 4.6 mo. Conclusion: For patients with MML, surgery with TIL should strongly be considered as it can result in prolonged survival in a highly selected group of patients.



Upper curve: OS with TIL therapy; survival plateaus at 65%. Lower curve: OS without TIL therapy; MS 4.6 mo.

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The Incidental Adrenal Mass: Correlation of Histopathology with Imaging L. Yip,[1]* J.L. Falcone,[1] M.E. Tublin,[2] C.R. Nordman,[2] M.T. Stang,[1] J.B. Ogilvie,[1] S.E. Carty,[1] J.H. Yim.[3] *1. Surgical Oncology, Endocrine Surgery, University of Pittsburgh, Pittsburgh, PA; 2. Department of Radiology, University of Pittsburgh, Pittsburgh, PA; 3. Department of Surgery, City of Hope, Duarte, CA.*

Introduction: Incidental adrenal masses are present in ~5% of patients who undergo cross-sectional imaging. Characteristics on computed tomography (CT) and magnetic imaging resonance (MRI) imaging may help distinguish benign adrenal adenomas. But, most studies rely on clinical follow-up as proof of the lesion's benign nature. We examined adrenalectomy results to determine if imaging characteristics correlate with histopathologic findings. Methods: We reviewed data for 210 adrenalectomy patients from 1/00-7/08 excluding

patients with pituitary or ectopic Cushing's syndrome or incomplete records to arrive at 168 consecutive adrenalectomies in 166 patients. The adrenal mass was considered benign on imaging with ≥1 of the following: Hounsfield Units <10 on unenhanced CT, contrast-enhanced CT quantifying absolute contrast washout of >60% or relative contrast washout of >40%, or MRI with chemical shift imaging demonstrating loss of signal intensity on out of phase images. Adrenocortical carcinoma (ACC) was diagnosed if capsular, vascular, or lymphatic invasion, and/or distant metastasis were present. Results: The sensitivity, specificity, and accuracy of preoperative imaging to distinguish benign adrenal lesions from non benign lesions were 59, 100, and 77%. Even among 75 adrenal masses ≥4 cm, the sensitivity, specificity, and accuracy were similar (57, 100, and 85%). Histopathology confirmed that 54 adrenal masses with benign imaging were benign. Malignant adrenal lesions were diagnosed in 16/114 (14%) masses with non benign imaging: 10 metastases, 4 ACC, 1 epithelioid angiosarcoma, and 1 ganglioneuroblastoma. The sensitivity of imaging in identifying malignancy was 100%. Post-operative follow-up identified no missed malignancies (mean 6 mos). Conclusion: Adrenal masses with benign CT or MRI characteristics are histopathologically benign with 100% specificity. Large adrenal lesions (≥4 cm) with benign imaging can be followed with initial short interval serial imaging and may not always need resection. In our series, no malignant lesion had benign imaging. To exclude malignancy, adrenal masses with non benign imaging characteristics should be resected.

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Micromedullary Thyroid Cancer: How Micro is Truly Micro?

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Introduction: The aggressive nature of medullary thyroid cancer (MTC) is evidenced by its propensity to present early with lymph node (LN) metastases. The clinical significance of non-familial MTC 1 cm in size or smaller (microMTC) is not clearly defined. We hypothesized that smaller tumors would be biologically less aggressive. **Methods:** We performed a retrospective review of the clinical, laboratory, and pathologic data for all patients treated or followed at our institution for microMTC from 1987 through 2008. **Results:** A total of 18 patients met criteria for inclusion in our study. Eight (44%) of the patients were women and the median age at operation was 58 (range: 32 – 76). None of the patients had a family history of MTC or multiple endocrine neoplasias, all tumors were unifocal, and C-cell hyperplasia was identified in only 2 (11%) patients. Fourteen (78%) patients underwent total thyroidectomy, while four (22%) had lobectomy with isthmusectomy alone. The median and mean tumor size was 0.53 cm (range: 0.1 to 1.0 cm). Four (22%) patients were found to have LN metastases. However, none of the 9 patients with tumors smaller than 0.5 cm in size had clinical evidence of LN metastases. Patients were followed for a median of 3.1 years (mean, 4.2 years) and there were no deaths. Pre-operative calcitonin levels were available for 7 patients. Post-operative calcitonin levels were available for 17 patients, of whom 13 have levels in the normal range (range: undetectable to 3.9 pg/ml). The four patients with elevated post-op calcitonin levels (range: 6.3 to 644 pg/ml) had tumors ranging from 0.7 to 0.9 cm in size. **Conclusions:** Tumors smaller than 0.5 cm are associated with a complete absence of clinically detectable nodal disease or elevated post-operative calcitonin levels in our series. In contrast, the high rate of LN metastases and elevated post-operative calcitonin levels in patients with microMTC greater that 0.5 cm in diameter suggests a similar biology to standard MTC. Our data suggest that the size definition of microMTC should be smaller than previously described.

Characteristics of Patients with MicroMTC

	Size < 0.5 cm (n=9)	Size > 0.5 cm (n=9)
Female:Male	2:7	6:3
Patients with LN Resected	1/9	5/9
LN Metastases Detected	0/1	4/5
Pre-operative Calcitonin Checked	1/9	6/9
Elevated Pre-operative Calcitonin	0/1	6/6
Post-operative Calcitonin Checked	8/9	9/9
Elevated Post-operative Calcitonin	0/8	4/9

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Recurrence of Adrenocortical Carcinoma Following Resection: Surgery Alone Can Achieve Results Equal to Surgery Plus Mitotane

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Background. Adrenocortical carcinoma (ACC) is a rare disease for which recurrence following surgery is common. A recent non-randomized inter-institutional study (NEJM 2007) reported that the addition of adjuvant mitotane to surgery for ACC was associated with a decreased recurrence rate (49% with mitotane vs 73-91% without mitotane). Because of limitations inherent in such a multi-institutional study, we investigated the influences of surgery and adjuvant mitotane in a large series of ACC patients evaluated and treated at a single tertiary care referral center. Study design. Retrospective evaluation of patients followed at a single institution after surgery for ACC. Results. 182 patients with ACC without metastasis underwent primary resection either at the index institution (surgery index [SI], n=26) or an outside institution (surgery outside [SO], n=156), after which they were referred to the SI. Median tumor size was similar in the two groups (11.5 versus 12 cm, p=.12). All SI patients underwent open resection; 12 SO patients underwent laparoscopic resection. After a median follow-up of 34 months, 145 patients recurred, including 10/26 (38%) SI and 135/156 (87%) SO patients. Disease-free (DFS) and overall survival (OS) were superior for SI versus SO patients (median DFS 28 vs 12 months, log-rank P=.005; median OS not reached vs. 37 months, log-rank P=.007). 11 patients received adjuvant mitotane, including 1 SI and 10 SO patients (all 11 recurred). For patients who did or did not receive mitotane, there was no difference in DFS (median 9 vs 12 months, P=.43) or OS (median 27 vs 43 months, P=.51). Conclusions. Contrary to the NEJM report, a recurrence rate of less than 50% can be achieved in ACC patients without the use of adjuvant mitotane. Although referral bias is partially responsible for the high rate of recurrence seen here in the SO group, these results suggest that differences in completeness of surgery, rather than adjuvant mitotane, may be primarily responsible for differences in ACC recurrence rates identified between institutions.

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Prognostic role of lymph-node involvement in patients undergoing neck dissection for medullary thyroid cancer

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Background: Medullary thyroid carcinoma (MTC) is a relatively rare cancer. In a period of increasing controversy regarding prophylactic neck dissection procedure for MTC, clarity about the possible relation between extent of neck dissection and survival is essential. This study investigated whether the total number of removed lymph nodes, negative nodes removed and the presence of invaded lymph nodes would prove to be independent prognostic factors for survival. METHODS: Data from patients with a diagnosis of MTC with active follow-up in the SEER (Surveillance Epidemiology and End Results) database from 1973 to 2004 were examined. After categorizing the study population based on lymph node examined and presence of positive nodes, survival estimate and hazard ratio were compared, the total number of examined lymph nodes and their pathological status were analyzed for their prognostic value in survival of these patients. Kaplan-Meier and Cox proportional hazards analyses were used for statistical analysis. RESULTS: Of 1149 patients identified with MTC, 593 patients had lymph node dissection data. 62% of patients were female, 87 % were white, and the mean age was 50.6 years. There were 265 patients with zero LNs examined, 139 with one or more LN examined and all negative LNs, and 189 with at least 1 positive LN. Those with LNs examined and all negative LN had the best survival; LNs examined and at least one positive LN had the worst survival, and zero LN examined was in between (p< 0.0001). Total number of examined LN was not associated with improving survival outcome (p=0.41). Total number of positive LN was associated with increased mortality (Hazards ratio HR=1.05); for every additional positive node the hazard increases 5%.Prognosis was very poor in patients with metastatic disease to cervical lymph nodes. (HR=11.7). CONCLUSIONS: Pathologic involvement of the cervical lymph nodes is a strong prognostic factor for survival in patients with MTC. However, total number of LN examined didn't affect survival outcome and extensive lymph node dissection may not improve survival outcome. These highly significant findings warrant further investigation.

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Surgeon Performed Ultrasound Can Predict Differentiated Thyroid Cancer in Solitary Thyroid Nodules A.A. Jabiev,* M.H. Ikeda, I.M. Reis, C.C. Solorzano, J.I. Lew. *DeWitt Daughtry Family Department of Surgery, University of Miami Leonard M. Miller School of Medicine, Miami, FL.*

Introduction: Surgeon performed ultrasound (SUS) features may predict differentiated thyroid cancer (DTC). This study determines SUS characteristics strongly associated with DTC in patients with solitary thyroid nodules. Methods: A retrospective review of 115 patients with solitary thyroid nodules who had SUS prior to thyroidectomy was performed. Patients were subdivided into two groups based on final pathology results: DTC (n=61) and benign disease (BD) patients (n=54). SUS features of thyroid nodules included: ultrasound size, type (solid, mostly cystic, mixed), calcifications (micro-, coarse, none), borders (irregular, regular), shape (taller > width), echogenicity (hyper-, hypo-, isoechoic). For SUS features, odds ratio (OR), confidence-interval (CI), and p-values are presented. Results: Of 115 operated patients, 53%(61/115) patients had DTC [papillary, 59%; follicular variant/papillary, 34%; Hürthle cell, 5%; and follicular, 2%] and 47%(54/115) patients had BD [hyperplastic, 56%; follicular adenoma, 31%; lymphocytic thyroiditis, 7%; and Hürthle cell adenoma, 6%]. Both DTC and BD groups were similar in terms of age, race, gender and tumor size (p>0.05). Univariate analysis showed hypoechogenicity more likely to be associated with increased risk for DTC [OR=5.44, 95%CI: 2.43-12.18, p<0.001] compared to hyper/isoechogenicity as well as irregular borders [OR=4.72, 95%CI: 2.12-10.50, p<0.001], and microcalcifications [OR=4.31, 95%CI:1.88-9.91), p<0.001] when compared to regular borders and coarse/no calcifications respectively. Using a multivariate model including the 5 SUS characteristics, hypoechogenicity [OR=4.27, 95%CI: 1.74-10.47, p<0.002], irregular borders [OR=3.10, 95%CI: 1.25-7.70, p<0.015], and microcalcifications [OR=2.65, 95%CI:1.04-6.76), p<0.05] had greater association with DTC when compared to hyper/isoechogenicity, regular borders and coarse/no calcifications. Conclusions: Among the several SUS features studied, hypoechogenicity, irregular borders and microcalcifications were most strongly associated with an increased risk for DTC, and may have additional clinical value in predicting DTC in patients with solitary thyroid nodules.

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Estrogen receptor bela is a tumor suppressor in thyroid cancer cells G.G. Chen,* A.C. Vlantis, Z. Qiang, C.A. Van Hasselt. *Chinese University of Hong Kong, Hong Kong, HK, China.*

INTRODUCTION: The incidence of thyroid cancer is much higher in females than in males. Epidemical and animal studies have suggested a role of female hormones in promoting the development of thyroid cancer. Our previous study has demonstrated that estrogen can significantly stimulate the proliferation of thyroid tumor cells. In this study, we hypothesize that estrogen activates the estrogen receptor beta (ERbeta) to inhibit the thyroid tumor cell growth. METHODS: The expression of ERbeta protein was examined in human thyroid cancer cells (follicular and papillary). The level of ERbeta was also measured in thyroid cancer tissues and non-tumor tissues. In addition to estrogen, ERbeta agonist (DPN) and siRNA were used to activate and block ERbeta respectievly. After the modulation of ERbeta, cell proliferation and apoptosis were measured. A number of apoptotic molecules (Bcl-2, Bax and caspase-8) were also determined to explore the possible molecular basis of ERbeta-mediated changes. RESULTS: ERbata protein level was significantly lower in the thyroid tumor tissues than the non-tumor tissues. The existence of ERbeta in thyroid tumor tissues was confirmed in thyroid cancer cells (follicular and papillary). Activation of ERbeta by its agonist DPN significantly decreased the proliferation of tumor cells in a dose-dependent manner. Furthermore, it sensitized the tumor cells to cell death stimulation (TNFalpa plus cycloheximide). In contrast, block of ERbeta by its siRNA markedly enhanced the proliferation of thyroid tumor cells and rendered them resistant to cell death stimulation. The activation and the inhibition of ERbeta were associated with opposite changes in Bcl-2 and Bax. With DPN, the level Bcl-2 protein was decreased but Bax was increased. ERbate knockout by its siRNA stimulated the expression of Bcl-2 but inhibit the level of Bax. Finally, we showed the caspase-8 activity was significantly decreased by ERbeta siRNA. CONCLUSIONS: Thyroid tumor cells expressed a low level of ERbeta. The activation of ERbeta induced apoptosis of tumor cells whereas the inhibition of ERbeta results is in favor of survival. Therefore, ERbeta appears to be a tumor suppressor in thyroid cancer cells.

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Impact of Hospital Volume on Surgical Outcomes for Head and Neck Cancer M.C. Cheung,[1]* L.G. Koniaris,[1] E.A. Perez,[1] M.A. Molina,[1] W.J. Goodwin,[1] R.M. Salloum.[2] *1. University of Miami Miller School of Medicine, Miami, FL; 2. University of Rochester, Rochester, NY.*

Impact of Hospital Volume on Surgical Outcomes for Head and Neck Cancer Michael C. Cheung, Leonidas G. Koniaris, Eduardo A. Perez, Manuel A. Molina, M.D.*, W. Jarred Goodwin, Rabih M. Salloum Objective: To define the prognostic significance of surgical center case volume on outcome for head and neck cancer (HNC). Methods: Florida cancer registry and inpatient hospital data were queried for head and neck cancer diagnosed from 1998 - 2002. Results: Of the 11,160 operative cases of HNC identified, 35.3% were treated at low-volume centers (LVCs) 32.7% in intermediate-volume centers (IVC) and 32.1% at high volume centers (HVC). A larger proportion of high-grade tumors (27.9%) and lesions over 30mm (39.7%) were resected at HVC ($p < 0.001$). The median survival was 61 months for HVC and 52 months for IVC and 47 months for LVC ($P < 0.001$). Univariate analysis demonstrated significantly improved survival at HVC for low, medium, and high grade tumors, small tumors (< 30 mm), and for cancers of the parotid, larynx and pharynx. On multivariate analysis, corrected for patient comorbidities, treatment at a HVC was a significant independent predictor of improved survival (HR = 1.25, $p = 0.001$). Conclusion: HNC patients treated at HVC have significantly better long-term survival and cure rates. Where possible, patients with large (>30 mm), high-grade or parotid, larynx and pharynx tumors should be evaluated and offered care at a high-volume center.

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The Utility of Intra-Operative PTH for Primary Hyperparathyroidism due to Multi-Gland Disease A. Cayo,* R.S. Sippel, S. Schaefer, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

Background: Surgical resection is the only curative therapy for patients with primary hyperparathyroidism (1HPT). Operative failure is most often due to unrecognized multigland disease (MGD), which compromises 15-20% of patients with 1HPT. The use of intra-operative PTH (ioPTH) monitoring is well established for single gland disease. Controversy remains over the utility of ioPTH in MGD, with concern for false positive results leading to prematurely concluding the operation and leaving behind abnormal parathyroid tissue, risking future recurrence. The aim of this study was to determine the utility of ioPTH monitoring for MGD. Methods: Between November 2000 and March 2008, data were prospectively collected on 755 patients with 1HPT who underwent parathyroidectomy. PTH samples were collected pre-incision, and then at 5, 10, and 15 minutes after excision of suspected abnormal parathyroid gland(s). Surgical cure was defined as a drop of greater than fifty percent in PTH level. Patients were clinically cured if they became normocalcemic postoperatively and remained so for 6 months. The data were analyzed to determine how accurately ioPTH predicted success or failure of parathyroidectomy. Results: Of the 755 patients, 163 (21.5%) were found to have MGD on pathology. Intraoperative PTH monitoring was used in 161 of these cases. In 146/161 cases (90.7%), the ioPTH level fell by at least 50% after removal of all suspected abnormal glands. All of these patients (100%) remained normocalcemic postoperatively. In 15/161 cases (9.3%), the PTH level did not fall by >50%. For 11/15 cases (73%), patients remained hypercalcemic postoperatively or had recurrence. However, in the remaining 4 cases, the patients became normocalcemic postoperatively despite failure of the PTH to fall by >50%. In each of these patients, PTH levels fell between 40-50%. Conclusions: IOPTH monitoring accurately predicted the success or failure of parathyroidectomy in 97.5%(157/161) of patients with MGD. A fall of the IOPTH by >50% can be used as a highly accurate predictor of cure in patients with MGD. Therefore, IOPTH monitoring is a very useful tool in patients with 1HPT and MGD.

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High Throughput compound screening identifies new differentiation-based therapies for dedifferentiated liposarcoma (DDLS)

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Introduction: Liposarcoma comprises approximately 25% of soft-tissue sarcomas and 50% of all retroperitoneal sarcomas. Despite an aggressive surgical approach over 80% of patients with DDLS will recur locally and 30% will metastasize to distant sites within 3 years of diagnosis. DDLS are not very responsive to conventional chemotherapy therefore we sought to develop a small molecule screening approach to identify compounds for potential differentiation and cytotoxic therapies in DDLS. Methods: In this pilot 3,119 molecule screen 3 cell lines (two DDLS cell lines- DDLS8817 and LPS141, and 1 adipose-derived stem cell line as a control) were seeded onto 384-well plates, incubated with compounds (10 uM standard concentration) and analyzed for induction of C/EBPα. Cells were fixed and stained with specific anti-C/EBPα antibody and then labeled with a secondary antibody. The nuclei were stained with Hoechst and imaged on a laser confocal microscope. Positive hits were defined as C/EBPα expression intensity exceeding the minimum threshold of 10% expression increase above baseline. Cytotoxicity was also evaluated. Results: 35 of 3,119 compounds were identified as positive inducers of C/EBPα, with 129 demonstrating cytotoxicity. All 35 positive hits for C/EBPα induction demonstrated corresponding cell line cytotoxicity although in some cases non-selective cytotoxicity (ie, both cell lines) was seen. Selective enhancement of C/EBPα with non-selective cytotoxicity was seen with 5 compounds in DDLS8817 and 12 compounds in LPS141. 2 compounds demonstrated selective C/EBPα enhancement and cytotoxicity in DDLS8817, with 13 in LPS141. Overlap was seen with 3 compounds that demonstrated induction and cytotoxicity effects in both cell lines. (Table 1) Conclusions: A high-throughput assay based on the immunofluorescent detection of nuclear CEBPα protein, an early regulator of differentiation, was developed and identified 35 small molecules. This gain-of-function screen will assist in the discovery of molecular therapeutic agents that may differ from cytotoxic agents in that they target specific signaling pathways driving dedifferentiation and apoptosis.

Table 1

Total compounds tested	3,119
Total compounds cytotoxic	129
Compounds positive for C/EBPα induction	35
Specific induction and cytotoxicity	
DDLS8817	2
LPS141	13
Induction with non specific cytotoxicity	
DDLS8817	5
LPS141	12
Induction and cytotoxicity both cell lines	3

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Disruption of CCR5-dependent homing of regulatory T cells inhibits tumor growth in a murine model of pancreatic cancer

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Tumors evade immune destruction by actively inducing immune tolerance through the recruitment of CD4+ CD25+ Foxp3+ regulatory T cells (Treg). We have previously described increased prevalence of these cells in patients with pancreatic adenocarcinoma, in particular in the tumor environment, but it remains unclear what mechanisms are involved in recruiting Treg into the tumor microenvironment. Here, we postulated that chemokines might direct Treg homing to tumor. Using gene expression, immunohistochemical and flow cytometric analyses, we show, in both human pancreatic adenocarcinoma and a murine pancreatic tumor model (Pan02), that tumor cells produce increased levels of ligands for the CCR5 chemokine receptor (in particular CCL5), and, reciprocally, that tumor-infiltrating CD4+ Foxp3+ Treg, compared with CD4+ Foxp3- T cells, preferentially express CCR5. When CCR5/CCL5 signaling was disrupted, either by reducing CCL5 production by tumor cells or by systemic administration of a CCR5 inhibitor (TAK-779), Treg migration to tumors was reduced by approximately 50% ($P<0.01$) and tumors were smaller than in control mice ($P<0.005$). Thus, this study demonstrates the importance of Treg in immune evasion by tumors, how blockade of Treg migration may inhibit tumor growth, and, specifically in pancreatic adenocarcinoma, the role of CCR5 in the homing of tumor-associated Treg. Selective targeting of CCR5/CCL5 signaling may represent a novel immunomodulatory strategy for the treatment of pancreatic cancer.

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Stromal Neuregulin-1 (NRG-1) induces ErbB3-mediated resistance to erlotinib therapy in pancreatic cancer

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Introduction: Erlotinib is an epidermal growth factor receptor (EGFR) inhibitor employed in the treatment of pancreatic cancer and its activity is modulated by EGFR-ErbB3 interactions. A unique aspect of the pancreatic cancer microenvironment is its pronounced desmoplastic reaction. Hypothesis: tumor stroma exerts paracrine stimulation of pancreatic cancer cell proliferation affecting response to anti-EGFR therapy. The influence of pancreatic cancer stromal fibroblasts on ErbB3 signaling was analyzed in the context of erlotinib treatment. Methods: We utilized 23 laser-capture microdissected human pancreatic carcinoma specimens to analyze the selective epithelial and stromal expression of EGFR, ErbB3, and their respective ligands, epidermal growth factor (EGF) and NRG-1. The effects of NRG-1 and erlotinib on tumor cell proliferation were analyzed in seven pancreatic cancer cell lines. Results: EGFR and ErbB3 transcripts were expressed by all tumors. Relative NRG-1 levels were significantly higher in stroma than specimen-matched pancreatic carcinoma cells, where it was absent in 65% of cases ($p<0.05$). NRG-1 was present in both normal and cancer stromal fibroblasts. NRG-1 was upregulated in cancer-associated fibroblasts as verified in primary fibroblast cultures established from fresh normal and cancerous pancreatic surgical specimens. Pancreatic cancer stromal localization of NRG-1 protein was confirmed by immunohistochemistry. In vitro, ErbB3 protein expression levels directly correlated with the extent of NRG-1-induced proliferation in 6 out of 7 pancreatic carcinoma cell lines ($p<0.05$). The anti-proliferative effects of erlotinib were abolished by simultaneous NRG-1 administration in all erlotinib-sensitive pancreatic cancer cell lines. Conclusions: Pancreatic cancer stroma secretes NRG-1. NRG-1 promotes pancreatic carcinoma cell ErbB3 signaling and provides an escape mechanism from EGFR inhibition with erlotinib.

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Tumor-derived VEGF regulates the recruitment of immune effector cells

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Introduction: Solid tumors consist of a diverse population of cells, including tumor, endothelial, and immune cells as well as fibroblasts. In general, tumor associated macrophages confer a negative prognosis in patients with breast cancer. Myeloid-derived suppressor cells (MDSCs) are a population of immature myelomonocytic cells that have been shown to suppress antigen-specific immunity and attract regulatory T cells, which promote tumor growth. We characterized the effect of anti-VEGF therapy on immune cell infiltration in a breast cancer xenograft model. Methods: 5 million MDA-MB-231 human breast cancer cells were injected into the mammary fat pad of SCID mice. Therapy was initiated in established tumors (150 mm3) and consisted of control or an anti-VEGF monoclonal antibody (mAb) regimen (250 μg/subcutaneous injection 2x/week). The mAbs used included bevacizumab, a humanized mAb specific for human VEGF; 2C3, a mouse mAb specific for human VEGF; or r84, a fully human mAb that binds human and mouse VEGF. Results: Anti-VEGF therapy inhibited tumor growth significantly. Furthermore, immunohistochemical analysis of tumor tissue demonstrated that anti-VEGF therapy reduced microvessel density and macrophage infiltration. In addition, there was a significant increase in neutrophil infiltration in tumors from all the anti-VEGF regimens. Interestingly, there was a significant decrease in the number of MDSCs in tumors from animals treated with r84 compared to control, but not with the other anti-VEGF therapies. Conclusion: We demonstrate that r84 is a unique fully human anti-VEGF mAb that is effective in reducing the growth of breast tumors implanted into SCID mice. Aside from reducing tumor microvessel density, mice treated with r84 had a reduction in macrophage infil-

tration and MDSCs into tumors. These findings further define the complex molecular interactions in the tumor microenvironment and provide a translational tool, which may be relevant to the treatment of breast cancer.

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Novel Mutant Smoothened in Hepatomas Can Activate Hedgehog Signaling J.K. Sicklick,[1]* J. Wang,[2] D.N. Watkins,[3] J. Huang,[2] W. Chen,[2] A.M. Diehl.[2] *1. Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; 2. Division of Gastroenterology and Duke Liver Center, Duke University Medical Center, Durham, NC; 3. Monash Institute of Medical Research, Melbourne, VIC, Australia.*

Hedgehog (Hh) activation results in pancreatic and biliary cancers. We, and others, have demonstrated that Hh signaling is also dysregulated in hepatomas. We showed that 1) overexpression of the Smoothened (Smo) proto-oncogene mediates c-myc expression, and that 2) Smo mRNA correlates with hepatoma size. We also identified a novel K575M (KM) Smo mutation adjacent to 2 known mutations (M1, M2). This led us to hypothesize that this mutation may also activate Hh signaling and be hepatocarcinogenic. METHODS: Smo gene sequencing was performed in 19 hepatomas and 4 hepatoma lines (Hep3B, HepG2, PLC/PRF/5, Huh7). Using real-time RT-PCR, mRNA expression of Hh components was compared between the KM tumor and 13 wild-type (Wt) tumors. Cloning of KM Smo (KMS) was performed in a pFLAG-CMV-3 vector. Comparisons were made with empty vector (EV) and vector containing Wt Smo (WTS). Hh transcriptional activity was evaluated in transfected C3H10T½ cells. AML-12 hepatocytic clones were generated with the constructs and xenografts were injected into athymic mice. RESULTS: One of 19 (5.3%) hepatomas and 0/4 hepatoma lines harbors the KM Smo mutation. The KM tumor had ≥2-fold higher expression of Hh target genes, Ptc and Gli1, in 27.3 and 81.8% of comparisons, respectively. Gli2, a hepatoma proliferation factor, was 36- to 107-fold higher in the KM tumor than Wt tumors. Cells transfected with KMS (N=9) had 30% higher Hh activity than cells with WTS (N=6, $P<0.05$). AML-12 clones with WTS and KMS overexpressed Ptc, Gli1, and Gli2 mRNA. However, all xenografted AML-12 cells failed to produce tumors at 6 wks (N=4). Similarly, Alb-Cre mice crossed with oncogenically mutated SmoM2-loxP mice did not develop hepatomas at 14 mos post-partum (N=15). CONCLUSIONS: The KM Smo mutation is infrequent in hepatomas but can activate Hh signaling. However, this mutation and another oncogenic Smo mutation did not induce hepatoma formation when overexpressed in mature hepatocytes. This may suggest that hepatocytes are not the likely culprits in hepatocarcinogenesis or that KM Smo is insufficient to induce tumors. It remains to be determined whether hepatic progenitors with Hh overactivation can undergo hepatocarcinogenic transformation.

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Detailed Analysis of the INSIGHT Global DNA Mismatch Repair (MMR) Gene Locus Specific Mutation Database (LDSB) and Familial Colorectal Cancer (CRC) A. Azarbayejani,[1]* J. Ady,[1] V. Lai,[1] J. Shin,[1] Z. Yuan,[6] P. Peltomaki,[2] G. Moeslein,[3] F. Macrae,[4] D. Sas,[1] N. White,[5] T. Weber.[1] *1. Surgery, Albert Einstein College of Medicine, New York, NY; 2. University of Helsinki, Helsinki, Finland; 3. St Josefs Hospital, Dusseldorf, Germany; 4. The Royal Melbourne Hospital, Melbourne, VIC, Australia; 5. Salanter-Akiva Riverdale High School, New York, NY; 6. Molecular Genetics, Albert Einstein College of Medicine, New York, NY.*

Introduction: InSiGHT (International Society for Gastrointestinal Hereditary Tumors) currently leads an effort to advance the gains of the Human Genome Project, focusing on DNA MMR gene LSDBs and familial colorectal cancer (CRC). The purpose of this report is to present a novel analysis of the InSiGHT LSDB (www.insight-group.org) that directly supports genomics research and clinical cancer genetics. Our report includes a MMR allele frequency analysis of MSH2, MLH1, MSH6, MLH3 & PMS2, relation to functional domains and includes all known MMR unclassified variants (UVs). Methods: We designed a relational database and performed a systematic analysis of all MMR gene sequence alterations associated with familial CRC and reported to the InSiGHT database. We included all pathologic and non-pathologic sequence variants including a novel set of MMR UVs. We compiled frequency distribution histograms of all reported sequence variations and mapped them to exon, codon and gene specific functional domains. Results: The total number of MMR gene sequence alterations reported to InSiGHT was 884 including 627 unique alterations and 101 UVs. 122 alterations were reported with a frequency of greater than once. The most frequently reported pathologic mutation was an A to T mutation at exon 5 of MSH2. The top 20 mutations were evenly split between MSH2 and MLH1. Allele specific report frequency including UVs correlated with functional domain location but was not a function of exon nucleotide length. Conclusions: Our results provide the first complete frequency analysis of DNA MMR gene sequence alterations reported to the InSiGHT LSDB. These data, including the identification of multiple UVs provide valuable information for genomics research and clinical cancer genetics. We now plan expansion of our analyses to include additional U.S. and international MMR gene LSDBs. We believe these efforts expand our understanding of important genotype-phenotype relationships in human CRC, directly support the goals of InSiGHT and the Human Variome Project, and provide a unique and valuable data set for genomics research, clinicians and patients.

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Resveratrol Activates Notch1 Signaling, Inhibits Cellular Proliferation, and Diminishes Neuroendocrine Markers in Pheochromocytoma M. Cayo,* A. Cayo, S. Jarjour, S. Pinchot, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

Introduction: The importance of the activity of the Notch1 signaling pathway in neuroendocrine (NE) tumors has recently become evident. Pheochromocytoma is a NE tumor of the adrenal medulla which causes debilitating symptoms secondary to excess catecholamine secretion. Surgery is currently the only curative treatment available. However, a significant proportion of patients present with unresectable disease, and although these patients can be palliated, novel curative therapies would represent significant advancement. Our high throughput quantitative screening for selective Notch1 pathway activators within the small-molecule library indicated that the naturally occurring compound resveratrol strongly activates Notch1 signaling. We hypothesized that resveratrol may activate Notch1 in pheochromocytoma cells and potentially inhibit cellular proliferation and NE marker expression. Methods: Pheochromocytoma (PC-12) cells were treated with increasing concentrations of resveratrol. MTT cellular proliferation assay was used to determine resveratrol's effect on cell growth. Expression of Notch1, NE markers, and apoptotic markers was studied using Western analysis. Results: PC-12 cells lack Notch1 activity at baseline. Resveratrol treatment led to a dose-dependent induction of expression of both the full-length Notch1 protein and the cleaved Notch1 intracellular domain. Induction of Notch1 signaling caused reduction of the important NE tumor markers ASCL1 and Synaptophysin, and a significant reduction in cellular proliferation. Caspase 3 was progressively cleaved to its active form with increasing resveratrol concentrations, indicating that the mechanism of the observed growth inhibition was apoptosis. The DNA repair enzyme PARP, a target of the activated caspase cascade, was also cleaved and inactivated with increasing doses of resveratrol, confirming the occurrence of apoptosis. Conclusion: Resveratrol activated Notch1 signaling, inhibited cellular proliferation, reduced expression of NE markers, and induced apoptosis in pheochromocytoma cells, suggesting its potential as a therapy for this disease in humans.

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Analysis of 14 circulating angiogenic factors in colorectal cancer patients using a multiplex array reveals profiles associated with nodal or distant metastasis U.N. Maduekwe,[1]* S. Connors,[2] C. Rothrock,[1] B. Reinschild,[1] S. Ryeom,[2] S.S. Yoon.[1] *1. Surgical Oncology, Massachusetts General Hospital, Boston, MA; 2. Children's Hospital, Boston, Boston, MA.*

INTRODUCTION: Elevations of circulating angiogenic factors in patients with colorectal cancer (CRC) have been shown to correlate with disease burden and prognosis. Recent technologies allow measurement of numerous angiogenic factors from a small blood sample. We sought to determine how levels of a broad range of angiogenic factors are associated with different levels of disease severity. METHODS: After informed consent, blood samples were collected prior to surgery and plasma was measured for the levels of 14 angiogenic factors using a quantitative array-based multiplex sandwich ELISA system. RESULTS: 53 patients (47.2 % female) with a median age of 68.5 years were enrolled. 40 lesions were in the colon and 13 were in the rectum. Patients

were categorized into three groups: Group 1 had adenoma or cancerous polyps completely excised at colonoscopy but required additional surgery (n=13), Group 2 had primary CRC (n=29), and Group 3 had metastatic CRC (n=11). There were no significant differences in any factor level between Groups 1 and 2. 12 of 14 factors were nominally higher in Group 3, but only PDGF-AA elevation reached statistical significance (p = 0.049). An adjusted total value (ATV1) was calculated for each patient using the 5 most elevated factors (ANG-1, ANG-2, HGF, PDGF-AA and PlGF), and this ATV1 was correlated with extent of disease in patients with primary versus metastatic disease (p=0.0199). Among Group 2 patients, HGF (p=0.038), PDGF-BB (p=0.032), PlGF (p=0.034), VEGF (p=0.047) were significantly higher in patients with stage I/II disease versus stage III disease. Another ATV (ATV2) calculated using these 4 factors was associated with node negative versus node positive primary disease with high significance (p=0.0128). CONCLUSIONS: In this exploratory analysis, circulating angiogenic factor profiles change as CRC progresses from primary tumors to nodal metastases and/or to distant metastases. Use of a multiplex array to determine the levels of numerous angiogenic factors may allow for the development of profiles that reliably predict extent of disease or prognosis.

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When Is Prophylactic Thyroidectomy Indicated For Patients With The *RET* C609Y Mutation? D. Calva,* T.M. O'Dorisio, M.S. O'Dorisio, G. Lal, S. Sugg, R.J. Weigel, J.R. Howe. *University of Iowa Carver College of Medicine, Iowa City, IA.*

BACKGROUND: Mutations in 5 cysteine codons (609, 611, 618, 620 and 634) of the *RET* extracellular domain cause MEN2A and familial medullary thyroid cancer. An international consensus statement recommends prophylactic thyroidectomy by the age of 5 for high-risk mutation carriers, but patients with codon 609 mutations appear to develop MTC at a later age, and there remains no consensus on the appropriate timing for prophylactic thyroidectomy. We report a 3 generation family with the C609Y *RET* mutation whose findings suggest that these patients may undergo thyroidectomy at a later age. **METHODS:** Ten family members with C609Y mutations underwent total thyroidectomy with or without central neck dissection. Clinical, laboratory, and pathological data were reviewed. A literature review of published codon 609 *RET* mutations was also carried out. **RESULTS**: Laboratory and pathology results of this family are summarized in the table. No patients had biochemical evidence of pheochromocytoma, and one patient had a parathyroid adenoma at exploration. The mean age at thyroidectomy was 39 (range 10-59 years). Six of 10 patients had MTC at a mean age of 49 (range 34-59 years); 4 of these 6 had lymph node metastases. One patient had C-cell hyperplasia (CCH) at age 37, and 3 patients had normal thyroid pathology found at ages 10, 13, and 36 years. All 6 patients with MTC had an elevated basal calcitonin (CT) level (nl. <11.5 pg/ml). In another large family reported with the C609Y mutation, 15 patients had MTC at a mean age of 42.3 years (range 21-59 years), and 6 patients had CCH (mean age of 24, range 15-37 years). **CONCLUSION:** Since the youngest patient in our family with C609Y *RET* mutations was diagnosed with MTC at 34 years of age, and the youngest patient reported in the literature was 21 years of age, current recommendations regarding the timing of prophylactic thyroidectomy for this mutation should be revisited. The available data suggest that these patients can delay thyroidectomy until the age of 10-15 years, with annual calcitonin testing prior to surgery.

PT#	Age	CT (pg/ml)	Pheo	HPT	Thyroid Pathology	Nodes
1	51	8332	No	No	MTC	0/39
2	59	39	No	No	MTC/CCH	7/29
3	40	23	No	No	MTC	0/25
4	13	3	No	No	Normal	N/A
5	10	2	No	No	Normal	0/4
6	57	202	No	No	MTC/CCH/PTC	8/40
7	36	4	No	No	Normal	0/18
8	54	294	No	No	MTC/CCH/PTC	1/35
9	37	8	No	No	CCH	0/10
10	34	762	No	Yes	MTC	9/18

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Colorectal Cancer in the Very Young: A Comparative Study of Tumor Markers, Pathology and Survival in Early Onset and Adult Onset Patients S.A. Khan,[1]* M. Morris,[2] K. Idrees,[1] M. Gimbel,[1] S. Rosenberg,[1] Z. Zeng,[1] J. Shia,[1] M. LaQuaglia,[1] P.B. Paty.[1] *1. Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; 2. University of Western Australia, Crawley, WA, Australia.*

Background: Colorectal cancer (CRC) diagnosed before age 30 is a rare and often fatal disease whose biology remains poorly understood. To better understand its pathogenesis, we compared tumor markers, immunohistochemistry (IHC) and clinical data in a large cohort of early-age onset and adult onset patients. Methods: Clinical data and archival tumor tissue were collected retrospectively from academic centers in the United States (US) and Australia for 94 patients treated surgically for early-age onset CRC (≤ age 30). These cases were compared to 276 adult onset patients (≥ age 50) treated surgically for CRC at a single institution in the US. Tumor tissue was assessed for morphology, microsatellite instability (MSI-H), microsatellite stability (MSS), mutations in Kras and Braf, and expression of mismatch repair (MMR) proteins (MSH2, MLH1, MSH6, PMS2). Results: The early-age onset group was distinguished from the adult onset group by multiple clinical, histological and molecular features (see table). MSI-H was associated with improved survival and loss of MMR gene expression in both age groups. However compared to the adult group, MSI-H in early-age onset CRC was more prevalent (p<0.01), not tightly linked to the loss of MLH1/PMS2 genes and never associated with Braf V600E mutations (p<0.01). The MSS/BrafV600E genotype was found to be a poor prognosis group at all ages but was more prevalent in the early-age onset group (9% vs. 4%). Conclusions: Specific genetic subtypes of CRC are found at different frequencies in early-age onset and adult onset CRC. Complete absence of the indolent course MSI-H/BrafV600E genotype and enrichment in the unfavorable MSS/BrafV600E genotype help explain the overall poor prognosis of early onset CRC.

Clinical, Histological and Molecular Features of Early-Age Onset and Adult Onset Colorectal Cancer

Characteristic	Age ≤30 (N=94)	Age ≥50 (N=276)	P
Median Age	27	67	-
Detection by screening test	0%	13%	<0.01
Family History of CRC	43%	27%	NS
Tumor Location: Proximal	34%	35%	NS
Advanced Stage: III + IV	76%	50%	<0.0001
Histology: Poorly Differentiated Mucinous Signet Ring	37% 12% 13%	8% 14% <1%	<0.0001 NS <0.00001
MSI-H	27%	13%	<0.01
Kras codon 12/13 mutation	28%	36%	NS
Braf V600E mutation	9%	8%	NS
5-year survival	48%	78%	<0.00001
Median Disease-Specific Survival(mo)	44	>120	<0.00001

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Asian-Americans Have Superior Outcomes for Gastric Adenocarcinoma B.A. Mailey,* C. Sun, A. Artinyan, C. Prendergast, A. Pigazzi, J. Ellenhorn, S. Bhatia, J. Kim. *City of Hope, Duarte, CA.*

Background: Survival for gastric cancer is reportedly higher in Asian nations than the United States. To examine potential racial disparities in survival, we assessed gastric cancer outcomes for a large heterogeneous U.S. population. Methods: Patients with gastric adenocarcinoma diagnosed and/or treated in Los Angeles county hospitals between 1988 and 2006 were identified from the comprehensive California Cancer Registry, Los Angeles County Cancer Surveillance Program (CSP). Patients were categorized by race as Asian, White, Black or Hispanic. Clinicopathologic characteristics were compared and survival differences between races were analyzed. Cox proportional hazard method was used to examine the effect of race on mortality. Results: Of 13,529 patients from CSP, 42% (n=5641) were White, 20% (n=2753) Asian, 25% (n=3367) Hispanic, 11% (n=1531) Black, and 1.8% (n=237) other. For the entire cohort, Asians demonstrated better overall survival compared to Whites, Black, and Hispanics (median survival, 15.8, 8.3, 7.8 and 8.5 months, respectively; all log-rank p-values < 0.001). Multivariate Cox regression analysis showed that Asian race controlling for age, sex,

tumor site, chemotherapy, radiotherapy, surgery, grade, and stage had improved chance of survival (HR 0.76, 95% CI: 0.72-0.80, p<0.001). From the entire cohort, 55.7% (n=7529) underwent surgical resection. Asians demonstrated significantly better survival after surgical resection compared to Whites, Blacks and Hispanics (median survival 31.5, 17.6, 17.8 and 19.1 months, respectively; all log-rank p-values <0.001). Cox regression analysis for surgical patients showed that Asians had better chance of survival after surgery (HR 0.79, 95% CI: 0.73-0.85, p<0.001). Conclusion: Asian-Americans with gastric adenocarcinoma have outcomes superior to Whites, Blacks or Hispanics. Since improved survival appears unrelated to surgical technique, survival disparities may be the result of other factors, e.g., tumor biology, and should be closely investigated in light of recent positive gastric cancer trials reported from Asian nations.

Figure 1a. Overall Survival by race for entire cohort

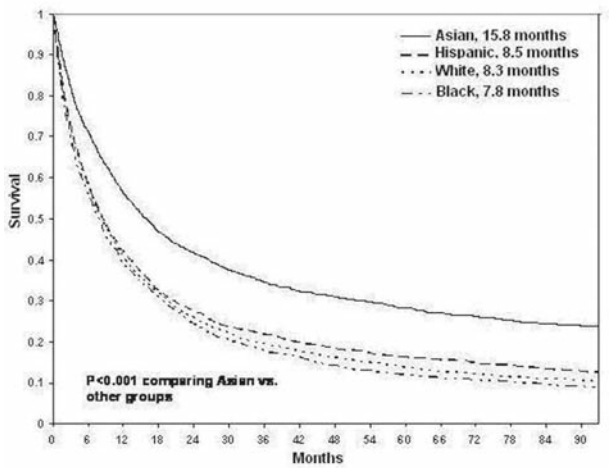
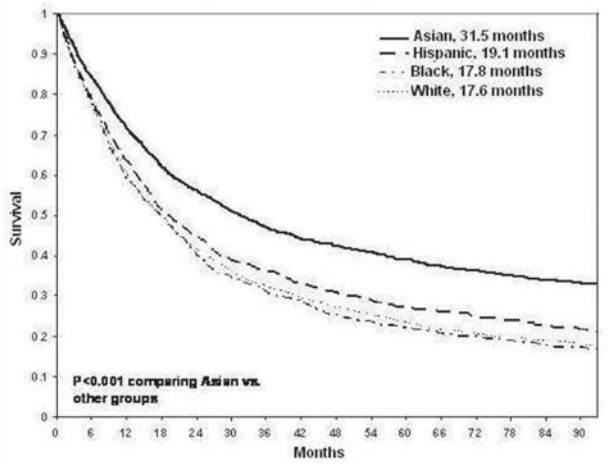


Figure 1b. Overall Survival by race for surgical patients.



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Positive Bone Marrow Biopsy is Associated with a Decreased Event Free Survival in Patients with Breast Cancer A. Mascaro,[1] C.E. Vitelli,[1] A. Baldi,[2] M. Farina,[1] M. Amini,[1] F. Piro,[1] L. Fortunato.[1]* *1. San Giovanni - Addolorata Hospital, Rome, Italy; 2. Federico II University, Napoli, Italy.*

Introduction: Bone marrow (BM) biopsy has been suggested as an independent prognostic tool to improve staging in patients with breast cancer. **Methods:** 266 patients operated for breast cancer from June 2000 to June 2008 were enrolled in this protocol after signing an informed consent. After primary surgery, BM aspirate from the iliac crest was obtained and 5-10 cc of blood collected. Since 2002 a peripheral blood (PB) sample was also obtained. Both CEA and Mammoglobin specific nested reverse transcriptase (RT) polymerase chain reaction (PCR) assays were used to examine BM and peripheral blood samples. Results were blind to physicians and patients. Nodal status (N)was defined after serial section analysis and immunohistochemistry of the sentinel lymph node. **Results:** 266 patients underwent BM and/or PB test. The median age of the patients was 56 years (34-80), and the median tumor diameter 1.5 cm (0.2-4.5). BM aspirates were unsuccessful in nine patients, RT-PCR was not technically feasible in 18 women, leaving 239 patients available for analysis of results and follow up. Among them 108 patients (45%) had either a BM or a PB test positive. At a median follow up of 60 months, 35 events (14%) occurred: 21 deaths,10 systemic and 5 loco-regional recurrences,and 1 new primary . Event-free survival was significantly lower in the BM+ group (84% vs 96% p= 0.004), while there was a trend towards diminished overall survival (90% vs 94%)(p=0.1). Event free survival for N-/BM- patients was 82/85 (96%), for N+/BM+ patients was 44/59 (75%), while patients with only one status positive (N-/BM+ or N+/BM-) had an intermediate disease free survival (84/95)(88%)(p=0.001). **Conclusions:** This study confirms that BM biopsy has an impact on event-free survival of patients with operable breast cancer. This may identify a substantial subgroup of patients N-/BM- who may not require adjuvant chemotherapy, as well as a subgroup N-/BM+ with a decreased survival who may need a more aggressive approach.

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A Molecular Signature of Clinical Risk in Patients with Colorectal Liver Metastasis (CLM) J. Yeh,[1]* A.S. Caudle,[2] L. McPhail,[1] C.S. Sigel,[1] L. Caskey,[1] E.D. Routh,[1] H.J. Kim,[1] M.O. Meyers,[1] B.F. Calvo.[1] *1. Division of Surgical Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC; 2. MD Anderson Cancer Center, Houston, TX.*

Despite recent advances in targeted therapy for patients with metastatic colorectal cancer (CRC), median survival is only 21 mos. Most CRC metastases affect the liver, thus, identification of genes involved in CLM has been of great interest. Although many gene expression signatures have been identified for CLM, none have been validated as a prognostic tool. Our aim was therefore to identify a prognostic gene signature for patients with CLM. Microarray analysis using Agilent whole genome arrays was performed on 53 CLM and 157 primary CRC tumors with clinically-annotated data. Significance analysis of microarrays was used to identify a gene signature associated with survival in the 53 CLMs. An independent dataset of 157 primary CRC from all AJCC stages was used as the testing dataset. The median survival of our 53 CLM patients was 27 mos with a median follow-up of 19 mos. Using a false discovery rate of 15% and an expected median number of false positive genes of 17, we identified a 119 gene signature in patients with CLM that predicts survival (41 vs. 21 mos, p=0.004). The only clinicopathologic variable significantly associated with survival was the clinical risk score (CRS) (p=0.02) in this training set. We then investigated the significance of this signature in an independent set of primary CRC. In primary CRC patients, our signature was associated with lymph node (LN) status (p=0.052) and LN ratio (positive LN/total number LN) using a cutoff of 0.08 (p=0.03). We report the first molecular signature of clinical risk in patients with CLM. This signature is equivalent to the CRS in predicting prognosis for CLM patients. In addition, our signature can be identified in primary CRC and is associated with nodal disease burden, a risk factor for metastatic disease, suggesting that primary tumors harbor molecular changes important in metastases. Therefore our molecular signature may identify key genes involved in not only metastasis, but also high-risk primary CRC. Further evaluation of this signature will provide critical insight into the development of novel therapies for CLM patients. Additional validation will be required to fully refine and test this new gene signature.

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Angiosarcoma: Clinical, pathological, and molecular predictors of Disease- specific survival in 222 patients G.J. Lahat,* A. Dukah, H. Halevi, L. Xiao, Z. Changye, K.D. Smith, J.A. Lazar, R.E. Pollock, D. Lev. *surgical oncology, MDACC, Houston, TX.*

Introduction: Angiosarcoma (AS) is a rare soft tissue sarcoma subtype exhibiting endothelial cell differentiation. We sought to identify clinical,

pathological, and molecular predictors of AS specific survival. Methods: Medical records of AS patients (n=222) treated at our institution from 1993 to 2008 were reviewed. An AS tissue microarray (TMA; n=70 human specimens) was constructed for immunohistochemical analysis of Ki67, p53, VEGF, D2-40, c-Kit, EGFR, and AKT signal transduction pathway activators. Univariable and multivariable analyses were used to identify independent disease specific survival (DSS) prognosticators. Results: Forty three (19.4%) metastatic patients and 179 (80.6%) patients with localized disease were included. Median survival of localized vs. metastatic AS was 49 (range, 2-188) vs. 10 (range, 1-69) months (p<0.0001). Patients with localized AS who underwent complete surgical resection (n=135; 75%) demonstrated significantly better outcome compared to those with unresectable tumors (n=44; 25%; p<0.0001). Of several factors identified as significantly adverse for DSS on univariable analysis, tumor size (>5cm vs. ≤5cm, p=0.01), high grade (p=0.012), and epithelioid histological component (0.008) remained significant on multivariable analysis as independent adverse DSS prognosticators in complete resection patients. Of the biomarkers evaluated in AS TMA, increased expression of AKT pathway activators, especially phospho-4EBP1 (an AKT/mTOR downstream target), was demonstrably associated with disease progression and was an independent risk factor for shortened DSS on multivariable analysis (p=0.05). Interestingly AKT pathway activation was more pronounced in radiation induced AS. Conclusions: Tumor size, grade, epithelioid component, and high levels of p-4EBP1 are independent predictors of adverse outcome in AS and should potentially be included in new AS-specific staging systems. In addition, the presence of highly expressed AKT pathway activators should be explored for utility as possible candidate AS personalized therapy targets.

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Histopathologic Basis for the Favorable Survival After Resection of Invasive Pancreatic Adenocarcinoma Associated With Intraductal Papillary Mucinous Neoplasm G.A. Poultsides,[1]* S. Reddy,[1] J.L. Cameron,[1] R.H. Hruban,[2] T.M. Pawlik,[1] N. Ahuja,[1] R.D. Schulick,[1] A. Jain,[1] B.H. Edil,[1] C.L. Wolfgang.[1] *1. Department of Surgery, Johns Hopkins Hospital, Baltimore, MD; 2. Department of Pathology, Johns Hopkins Hospital, Baltimore, MD.*

INTRODUCTION: Invasive pancreatic adenocarcinoma arising in the setting of Intraductal Papillary Mucinous Neoplasm (IPMN) is associated with better survival after resection than standard pancreatic ductal adenocarcinoma (PDA) in the absence of IPMN. We analyzed pathologic features that could account for this difference. METHODS: A single institution's prospective pancreatic resection database was retrospectively reviewed to identify patients with invasive pancreatic adenocarcinoma who underwent pancreatectomy with curative intent. Log rank and Cox regression analysis were used to identify factors associated with survival. RESULTS: Over a 12-yr period (1995 - 2006), 1260 consecutive patients were identified, 132 (10.5%) with IPMN-associated invasive adenocarcinoma and 1128 (89.5%) with standard PDA. Median follow-up for survivors was 30 months. Median disease-specific survival was 43 months after resection for IPMN-associated vs 19 months for standard PDA (P < 0.001). Median tumor size was 3.0 cm for both groups. However, compared to standard PDA, invasive adenocarcinoma arising within an IPMN was associated with a lower incidence of (1) regional lymph node metastasis (78% vs 51%, P < 0.001); (2) poor tumor differentiation (44% vs 26%, P < 0.001); (3) vascular invasion (54% vs 33%, P < 0.001); (4) perineural invasion (92% vs 63%, P < 0.001); and (5) microscopic margin involvement (28% vs 14%, P < 0.001). Specifically, in the presence of any one of the aforementioned adverse pathologic characteristics, outcomes after resection for IPMN-associated and standard PDA were not significantly different (Table). In fact, on multivariate analysis, tumor grade (P < 0.001), microscopic margin status (P < 0.001), tumor size (P = 0.001), and lymph node metastasis (P = 0.005), but not association with IPMN (P = 0.323), each were independently predictive of survival after resection. CONCLUSIONS: The favorable biologic behavior of IPMN-associated compared to standard PDA is based on its inherently lower rate of lymph node metastasis, high tumor grade, positive resection margin, perineural and vascular invasion.

		Median Disease-Specific Survival (Months)		P value
		IPMN-Associated Adenocarcinoma	Standard PDA	
Lymph Node Metastasis	No	92	25	<0.001
	Yes	20	18	0.441
Poor Differentiation	No	45	23	0.009
	Yes	23	14	0.099
Microscopic Margin Involvement	No	53	21	<0.001
	Yes	23	15	0.722
Vascular Invasion	No	65	23	<0.001
	Yes	23	18	0.646
Perineural Invasion	No	92	27	0.003
	Yes	25	18	0.211

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Colorectal cancer cells enriched for the cancer stem cell phenotype generate a soluble factor that mediates tumor cell growth and chemoresistance D. Bose,[1]* N. Dallas,[2] F. Fan,[1] L. Xia,[1] P. Gaur,[1] S. Samuel,[1] L.M. Ellis.[1] *1. MD Anderson Cancer Center, Houston, TX; 2. Northwestern University Feinberg School of Medicine, Chicago, IL.*

INTRODUCTION: We previously observed that oxaliplatin-resistant (OxR) HT29 colorectal cancer (CRC) cells had features of cancer stem cells (CSCs). We hypothesized that OxR cells and CSCs generate soluble factors that mediate growth and/or chemoresistance in chemosensitive CRC cells. METHODS: To generate CSC-enriched cultures, HT29 CRC cells were sorted for the side population (Hoechst 33342 efflux) as a functional assay for the CSC phenotype. Sorted cells were grown in sphere culture (serum-free media, low adhesion plates) to further select for the CSC phenotype, and then placed in standard adherent culture. Conditioned media (CM) was collected from these cells as well as parental and OxR HT29 CRC cells. Parental CRC cells were grown in CM from parental cells (HT29 CM), OxR HT29 cells (OxR CM), and cells enriched for CSCs (CSC CM) to determine the effects of soluble factors on CRC cell proliferation and chemoresistance. For co-culture experiments, luciferase expressing HT29 cells were co-cultured with OxR cells or control cells. Cell growth/survival of parental HT29 cells was determined by relative luciferase activity. RESULTS: OxR CM stimulated growth of parental HT29 and HCT116 CRC cells (2-4-fold) when compared to cells grown in HT29 CM. Co-culture of luciferase-labeled HT29 cells with OxR HT29 cells resulted in a 2-fold growth increase over co-culture with HT29 parental cells. Parental HT29 cells exposed to OxR CM demonstrated resistance to oxaliplatin compared to controls. In co-culture experiments, co-incubation of OxR cells with parental cells led to increased luciferase activity in parental cells after exposure to oxaliplatin. CSC CM stimulated cell proliferation (~2-fold) in both HT29 and HCT116 parental cells. Chemosensitive HT29 parental cells incubated with CSC CM were resistant to oxaliplatin treatment. CONCLUSIONS: OxR HT29 cells and CSC-enriched cell cultures generate soluble factors that mediate CRC growth and chemoresistance. Soluble factors from a minority of chemoresistant cancer stem cells may support the growth/chemoresistance of nearby tumor cells in a paracrine fashion.

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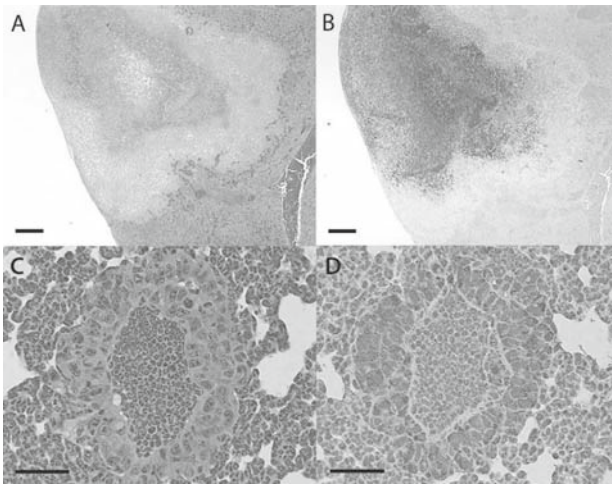
Attenuated Salmonella typhimurium Effectively Targets Breast Cancer Metastases S. Ganai,[1]* R.B. Arenas,[1] J.P. Sauer,[2] B. Bentley,[3] N.S. Forbes.[2] *1. Baystate Medical Center / Tufts University School of Medicine, Springfield, MA; 2. University of Massachusetts, Amherst, MA; 3. Pioneer Valley Life Sciences Institute, Springfield, MA.*

Introduction: Attenuated Salmonella typhimurium has remarkable tumor-targeting capabilities in part because it is attracted to heterogeneity in tumor microenvironments. In order to test the hypothesis that bacteria can accumulate in tumor independent of significant necrosis or hypoxia, we investigated whether S. typhimurium accumulates within microscopic and macroscopic metastatic lesions. Methods: A syngeneic metastasis model was used with Balb/c mice bearing subcutaneous 4T1 mammary tumors. After 21 days tumor growth, mice were intravenously infected with the msbB- purI- S. typhimurium strain. Primary tumors and their hepatic and pulmonary metastases were collected six days later. Bacterial culture and Salmonella immunohistochemistry were performed, with quantitative image analysis using Image J (National Institutes of Health). Results: Bacterial colonization was confirmed within primary tumors (mean, 4.2 x 10^6 cfu/g; 95% CI, 3.3 – 5.0 x 10^6 cfu/g) and their observed hepatic and pulmonary metastases. Quantitative image analysis demonstrated bacterial colonization within 44% of the cross-sectional area of

liver metastases (mean, 5.3 mm^2; 95% CI, 3.9 – 6.7 mm^2), compared to 0.5% ($p<0.05$) within normal hepatic parenchyma. Small pulmonary metastases less than five cells thick also demonstrated bacterial colonies. Conclusions: Despite a lack of necrosis within micrometastatic lesions, retained tumor-targeting capability was demonstrated, suggesting alternative mechanisms for bacterial accumulation within metastases including 1) nutrient gradients, 2) coupled transport via tumor embolism, 3) enhanced proliferation secondary to compartmentalization in metastatic cells, and 4) decreased clearance in an immunosuppressed environment. Further exploration of attenuated Salmonella typhimurium as a vector in the setting of metastatic disease is warranted to enhance its potential as an imaging modality and cancer therapeutic.



A and B, H&E and Salmonella immunohistochemistry (IHC) of contiguous sections of a metastatic lesion to the liver. Bar, 250μm. C and D, H&E and Salmonella IHC of contiguous sections of a perivascular pulmonary metastasis. Bar, 50μm.

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Tacrolimus Inhibits the Growth of Angiosarcoma in Mice
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Introduction: We recently discovered a novel angiogenesis factor, secreted frizzle-related protein 2 (SFRP2), that stimulates angiogenesis via the calcineurin/ NFAT signaling pathway. Tacrolimus (FK506) is an immunosuppressive drug that inhibits nuclear translocation of NFAT. We hypothesize that pharmacologic inhibition of NFAT should inhibit SFRP2 induced angiogenesis and tumor growth. Methods: Immunohistochistry with antibodies to SFRP2 and NFAT were performed on paraffin-embedded sections of human angiosarcoma. Protein lysates of SVR mouse angiosarcoma cells were collected and Western blot analyses was performed probing for SFRP2. Mouse endothelial cells were treated in a Matrigel tube formation assay with SFRP2 (30nM) with and without tacrolimus in vitro. To determine the antitumor activity of tacrolimus, SVR (1 million) cells were injected into the flank of 6-week-old nude male mice. Treatment was initiated on the day after inoculation. Mice received 3 mg/kg/daily i.p. tacrolimus or vehicle control. Serial caliper measurements of perpendicular diameters were used to calculate tumor volume using the following formula: (shortest diameter)squared X (longest diameter) x 0.52. The data were analyzed by a one-sided Student's t test. A P value of ≤ 0.05 was statistically significant. Results: 9/9 human angiosarcomas stained strongly positive for SFRP2, and 6/8 tumors stained positive for NFAT. Western blot analyses showed expression of SFRP2 in SVR mouse angiosarcoma protein lysates. Tacrolimus (1μM) inhibited SFRP2 induced mouse endothelial cell tube formation by 64%± (0.002). Treatment with tacrolimus (n = 4) for 20 days was effective at suppressing the growth of SVR angiosarcoma tumor in nude mice as compared with control (n = 4) mice. The groups were significantly different (P =0.04) at the end of the study on day 20, with a 57% suppression of tumor volume. Conclusion: SFRP2 and NFAT are strongly expressed in human angiosarcoma, and SFRP2 is expressed in the SVR mouse angiosarcoma tumor cell line. Tacrolimus inhibited SFRP2 induced endothelial cell tube formation in vitro, and the growth of angiosarcoma in vivo. A Phase II study of tacrolimus in angiosarcoma should be considered.

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A Novel Small Molecule Inhibitor Decreases Growth of Human Pancreatic Cancer Xenografts
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Introduction: Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase that is overexpressed in many types of tumors, including pancreatic cancer, and aids in tumor cell resistance to treatment and survival. Therefore, FAK is an excellent potential target for anti-cancer therapy. Since, specific small molecule kinase inhibitors of FAK have been difficult to obtain, we hypothesized that a novel and effective inhibitor could be identified using in silico modeling. Methods: Following Lipinski rules, 250,000 small-molecule compounds whose precise structures were known, were docked into the N-terminal domain of FAK in 100 different orientations using the DOCK5.1 computer program. The top scoring compounds were obtained from the National Cancer Institute Developmental Therapeutics Program. We identified and tested the effect of a novel leading small molecule inhibitor, 1,2,4,5-benzenetetraamine tetrahydrochloride (Y drug) targeting the main autophosphorylation site of FAK on human pancreatic cancer cell (Miapaca-2, Panc-1) biochemistry, cell viability, adhesion, apoptosis and tumor growth in vivo. Results: Y drug at doses of 1-100 μM specifically blocked phosphorylation of Y397-FAK and total phosphorylation of FAK. It directly inhibited FAK autophosphorylation in a dose-dependent manner. Furthermore, Y drug significantly ($p<0.05$) increased cell detachment and inhibited cell adhesion and viability in a dose-dependent manner. PARP and caspase-3 cleavage were noted in pancreatic cancer cells starting at doses of 5 μM. Y drug (30 mg/kg via intraperitoneal injection (IP) daily) effectively and significantly caused pancreatic tumor regression in vivo, when administered alone and its effects were synergistic with IP gemcitabine (30mg/kg) chemotherapy. This was accompanied by decreased proliferation (Ki67 staining) and increased apoptosis (caspase-3 staining) in the tumors treated with Y drug. Conclusions: Targeting the Y397 autophosphorylation site of FAK in pancreatic cancer with the small molecule inhibitor, 1,2,4,5-benzenetetraamine tetrahydrochloride, deserves further investigation as a novel treatment strategy in pancreatic cancer.

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Downregulation of the Tumor Supressor Gene Cyclin Dependent Kinase 2-Associated Protein 1 (CDK2-AP1) in Microsatellite Unstable (MSI) Human Colorectal Cancer (CRC) is Associated with Hypermethylation of the CDK2-AP1 Promoter
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Introduction: We have extensively studied and previously reported down regulation of the growth suppressor gene CDK2-AP1 in MSI CRC is strongly associated with DNA mismatch repair (MMR) deficiency. However the mechanism of this association remains unexplained and is a focus of our ongoing work. Our current study tests the hypothesis that CDK2-AP1 down regulation in MSI CRC is mediated by promoter hypermethylation. Methods: To study promoter methylation status we performed bisulfite conversion of the MSI cell line LIM1215, 2 ex vivo MSI colon cancers (T66, T99) and 2 microsatellite stable (MSS) cell line controls (Colo302, SW480). PCR amplification of the CDK2-AP1 promoter was followed by quantitative methylation analysis using MassARRAY of all 5 samples. To directly assess methylation status at CpG16 and 24 we performed direct sequencing of the CDK2-AP1 promoter on Lim1215 (MSI) and the SW480 (MSS) cell line control. Results: MassARRAY analysis of the CDK2-AP1 promoter demonstrated significant (>5%) methylation at CpG16 and CpG24 in the MSI line LIM1215 and both MSI tumors but no significant methylation at these sites or any other regions of the promoter in the MSS cell line controls (Colo302, SW480). In addition, direct sequencing confirmed CpG methylation at sites 16 and 24 in LIM1215 (MSI) but not in the MSS control cell line SW480. Conclusions: These novel results demonstrate significantly increased methylation of the CDK2-AP1 promoter

in a MSI cell line and multiple MSI colon cancers compared to MSS cell line controls. This finding supports the hypothesis that down regulation of CDK2-AP1 in MSI CRC is associated with increased methylation of the promoter region. We plan further analysis of this phenomenon in larger study sets. The precise mechanism of MMR deficient mediated promoter methylation will be our next area of investigation.

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Expression Profile of Pancreatic Cancer-Associated Fibroblasts Is Distinct From Carcinoma Cells R.F. Hwang,* T. Moore, A. Rivera, D.B. Evans, C.D. Logsdon. *Surgical Oncology, U.T.M.D. Anderson Cancer Center, Houston, TX.*

Introduction: We have recently shown that pancreatic cancer-associated fibroblasts (pancreatic stellate cells, PSCs) promote tumor growth and metastasis in vitro and in vivo. In order to identify the PSC-derived factors that may be responsible for these tumor promoting effects, we analyzed the gene expression profile of PSCs. **Methods**: Primary human PSCs were isolated from surgically resected pancreatic adenocarcinoma. To specifically identify genes expressed only by PSCs, microarrays (Illumina) were used to profile PSCs and three pancreatic cancer cell lines (Bxpc3, Panc1, and L3.6pl). We selected genes that were highly expressed in PSCs compared with cancer cells (>5-fold) and common gene functional classes were determined using DAVID gene functional classification tool. **Results**: This strategy yielded over 7000 genes that were uniquely expressed in PSCs but not in pancreatic cancer epithelial cells. The main gene category pathways were: cytokine (e.g.-tumor necrosis factor, platelet-derived growth factor receptors-alpha and beta, VEGF B and C), MAPK pathway (e.g.-brain derived neurotrophic factor, nerve growth factor beta), focal adhesion (e.g.-integrins, collagens, laminin), TGF-beta signaling, and complement and coagulation cascade. Other genes expressed by PSCs were related to type I diabetes mellitus, melanoma and prostate cancer. The expression of genes in each of these pathways was confirmed by RT-PCR. **Conclusions**: Pancreatic stellate cells promote the malignant phenotype of pancreatic adenocarcinoma. This study is the first comprehensive analysis of the gene expression profile of PSCs that may provide a basis for novel stromal-targeted therapies for pancreatic cancer.

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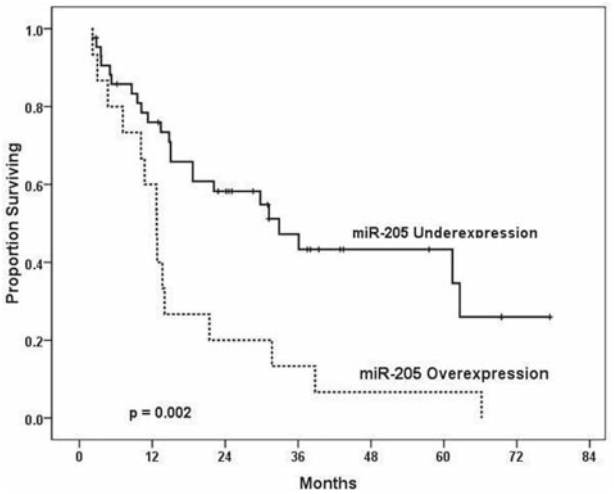
Overexpression of Micro-RNA 205 is a Predictor of Poor Survival in Esophageal Adenocarcinoma M.E. Dillhoff,* J. Liu, W. Frankel, S. Volinia, C. Croce, M. Bloomston. *Surgery, Ohio State University, Columbus, OH.*

Background: MiRNAs are small, noncoding RNAs (~20-22 nucleotides) that have been shown to have critical functions in the development of a variety of malignancies. A link between expression and survival has been sought for many miRNAs, including miR-205. The objectives of this study were to identify a global expression pattern for esophageal adenocarcinoma and to determine the impact of miR-205 expression on patient survival after esophagectomy. Methods: RNA was isolated from 61 resected esophageal adenocarcinomas and adjacent normal epithelium and hybridized to a miRNA microarray chip. Differentially expressed miRNAs between normal and malignant tissue were determined by significance of analysis of microarrays (SAM) and confirmed by quantitative real time PCR (qRT-PCR). Clinical data was obtained on all patients and survival curves created using the Kaplan-Meier method and compared by Log-rank analysis. Results: 39 miRNAs were found to be differentially expressed between adenocarcinoma and normal epithelium: 14 overexpressed and 25 underexpressed. MiR-205 demonstrated a five-fold decrease in tumoral expression by microarray ($p<0.05$) as well as decreased expression in 60% of tumors by analyzed by qRT-PCR. MiR-205 expression, nodal metastases, and preoperative weight loss resulted in decreased survival by univariate analysis. Only miR-205 expression (median 12.7 months vs. 32.9, p=0.002, Figure) and nodal metastases (10.7 months vs. 62.6, $p<0.001$) remained significant by multivariate Cox Proportional Hazards analysis. Hi miR-205 expression did not correlate with tumor size, differentiation, nodal status or T stage. Conclusions: A distinct miRNA expression pattern is able to discriminate esophageal adenocarcinoma from normal epithelium. As expected, nodal metastases were predictive of poor survival. Although miR-205 is typically underexpressed in esophageal cancer, when it is expressed, it portends a poor prognosis.



Kaplan Mier Survival Curve for Patients with Increased MiR-205

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Extended Preoperative Chemotherapy does not Improve Pathologic Response and Increases Postoperative Liver Insufficiency after Hepatic Resection for Colorectal Liver Metastases D. Zorzi,[1]* Y. Kishi,[1] D.M. Maru,[1] H. Wang,[1] D. Ribero,[2] E. Motta,[2] N. Ravarino,[2] M. Risio,[2] S.A. Curley,[1] E.K. Abdalla,[1] L. Capussotti,[2] J.N. Vauthey.[1]
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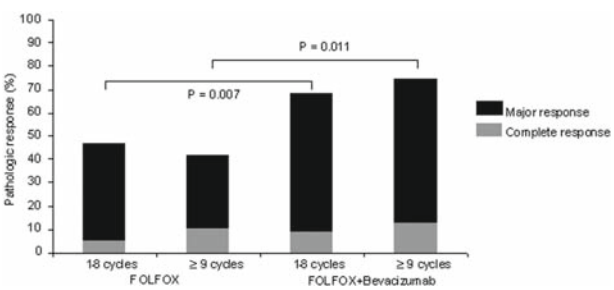
Introduction: The optimal duration, safety, and benefit of preoperative chemotherapy in patients with colorectal liver metastases (CLM) is unclear. The aims of the study were to evaluate the association between the duration of preoperative chemotherapy with 5-FU and oxaliplatin (FOLFOX) with or without bevacizumab and (1) pathologic response and (2) hepatotoxicity after hepatic resection for CLM. Methods: A total of 219 patients who underwent hepatic resection following FOLFOX with or without bevacizumab were divided into two groups according to the duration of chemotherapy: 1-8 cycles (short group; N = 157) and ≥ 9 cycles (long group; N = 62). The frequencies of complete or major pathologic response (<50% viable tumor cells), sinusoidal injury, and postoperative liver insufficiency (peak bilirubin > 7 mg/dL) were compared between the two groups. Results: Clinical, surgical, and pathologic variables were similar between the two groups. The proportion of patients who had complete or major pathologic response was 57% in the short group and 55% in the long group (P = 0.738). The combination of FOLFOX and bevacizumab was associated with a significantly higher frequency of complete or major pathologic response than FOLFOX alone in both the short and long groups (figure). The incidence of sinusoidal injury was higher in the long chemotherapy group (26% vs. 42%; P = 0.017), as was the incidence of liver insufficiency (4% vs. 11%; P = 0.035). Multivariate analysis revealed ≥ 9 cycles of chemotherapy as the only independent predictor of postoperative liver insufficiency (P = 0.031; odds ratio = 3.90). Conclusion: Extended preoperative chemotherapy increases the risk of hepatotoxicity after hepatic resection for CLM. The type of chemotherapy (FOLFOX plus bevacizumab) has more impact on pathologic response than does the duration of chemotherapy.



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CD8 T Cell Infiltrate Predicts Disease-Specific Survival Following Resection of Colorectal Cancer Liver Metastases S.C. Katz,* V.G. Pillarisetty, J. Shia, C. Hedvat, Z.M. Bamboat, M. Gonen, W.R. Jarnagin, P.J. Allen, Y. Fong, L.H. Blumgart, M.I. D'Angelica, R.P. DeMatteo. *Memorial Sloan-Kettering Cancer Center, New York, NY.*

INTRODUCTION: Tumor infiltrating lymphocytes (TILs) in primary colorectal cancer have been shown to independently predict survival. The prognostic importance of TILs in colorectal cancer liver metastases (CRCLM) has not been previously defined. We hypothesized that increased numbers of CD8 T cells would correlate with improved survival. **METHODS:** Patients who survived less than two or more than ten years following CRCLM resection were included. TILs were analyzed using tissue microarrays and immunohistochemistry. Optimal cutoff points for TIL numbers were determined using maximal chi square analysis. Correlation between TIL frequency and survival was determined using Kaplan-Meier or chi-square analysis. **RESULTS:** Of 163 patients, 105 survived less than 2-years and 58 survived at least 10-years. The average age was 62 years (range, 28-82) and 66% were male. Independent predictors of 10-year survival following CRCLM resection included $CD8^+$ TIL (cytotoxic T cell) number, CEA level, tumor size, tumor number, primary tumor nodal status, and extrahepatic disease ($p<0.05$). Of the patients with a high number of $CD8^+$ TILs, 69% survived 10 years or more, while 92% of patients with a low number of $CD8^+$ TILs survived less than 2-years ($p<0.01$). Disease-specific survival (DSS) for patients with higher numbers of $CD3^+$ (all T cells) or $CD8^+$ TILs was significantly longer than those who had low numbers of these cell types (table). A multivariate model demonstrated that a high number of $CD8^+$ TILs was an independent predictor of prolonged DSS ($p<0.01$, table), as was a clinical risk score of less than 3. The number of $CD45RO^+$ TILs (effector memory T cells) was not a significant predictor of DSS. Importantly, the ability of $CD8^+$ TIL number to predict DSS was significant at numerous cell number cutoff points. **CONCLUSIONS:** This is the first study to demonstrate that the number of TILs within CRCLM is an independent predictor of long-term survival following liver resection. The recruitment or expansion of $CD8^+$ TILs in CRCLM may represent a novel strategy for immunomodulatory therapy.

Factor		Mean DSS (Months)	Univariate *p*	Multivariate *p*	HR (95% CI)
$CD8^+$ TILs	HI	128.7	**<0.01**	**<0.01**	2.9(1.3-6.5)
	LO	70.9			
$CD3^+$ TILs	HI	124.0	**0.03**	0.25	1.7(0.7-3.9)
	LO	76.8			
$CD45RO^+$ TILs	HI	84.3	0.35	-	-
	LO	56.7			
Clinical Risk Score	1-2	113.4	**<0.01**	**<0.01**	2.7(1.8-4.0)
	3-5	38.1			

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Survival Benefits After Sentinel Lymph Node Mapping in Colon Cancer as Compared to Conventional Surgery S. Saha,* S. Sirop, A. Korant, B. Chakravarty, N. Krishnaiah, D. Panjam, D. Wiese, M. Arora, D. Eilender, T. Singh. *McLaren Regional Medical Center, Michigan State University, Flint, MI.*

Introduction: Sentinel Lymph Node Mapping (SLNM) in colon cancer(CCa) has been evaluated in multiple studies with high success rates, sensitivity and overall accuracy. We aimed to compare the survival of patients(pts) undergoing standard oncological resection along with SLNM at the time of surgery to pts without SLNM. **Methods:** Staging and survival analysis from our prospective database(gpA, 167 pts) were compared to the Surveillance, Epidemiology and End Results(SEER) database(gpB, 126,484 pts) from 1996-2003. All pts had invasive CCa. GpA pts underwent SLNM plus complete oncological resection. The minimal follow up was 5 years and the primary outcome was cancer related death.. Exclusion criteria for survival analysis in both groups included stage IV disease, development of 2nd cancer, refusal of indicated chemotherapy, or pts lost to follow up. **Results:** In gp A, SLNM was successful in 99.7%, with a sensitivity of 85.3%, negative predictive value of 91.7% and false negative rates of 14.6%. In 15.1% of pts, the disease was upstaged because of the presence of micrometastasis(0.2-2mm). The recurrence rates were 4.1% in stage I, 8.6% in stage II and 15.5% in stage III. The median follow up was 83 months. Of the 167 gpA pts, 39 pts were excluded(18 had stage IV, 9 had 2nd cancer and 12 refused chemotherapy) leading to the inclusion of 128 pts, of which 17(13.3%) pts lost to follow-up. In gp B, 89,483 pts were included in the analysis, of which 47,168 lost to follow up (table1). The average number of lymph nodes examined was 15.0 LNs/pt in gpA vs 12.5 LNs/pt in gpB($p=<0.0001$). The 5 year cancer-specific survival of pts in gp A as compared to gp B was **100% vs 94.9%** in stage I, **91.2% vs 83.5%** in stage II and **81.8% vs 63%** in stage III disease. **Conclusion:** SLNM is highly successful, sensitive and accurate in CCa. It upstages a significant number of pts and identifies pts with true node negative disease leading to improved disease specific survival as compared to conventional surgery. This study provides the first evidence of the impact of stage migration in CCa pts who underwent SLNM vs those who don't.

Table1: Comparison of the cause specific survival between patients that underwent SLNM with patients that underwent conventional surgery (SEER database).

Stage	SLNM			Conventional (SEER)			
	Total # of pts included	Lost to follow up *	5-year disease specific survival	Total # of pts included	Lost to follow up *	5-year disease specific survival	
I	37	4	**100%**	25,593	15,090	**94.9%**	0.21
II	46	5	**91.2%**	34,813	19,071	**83.5%**	0.16
III	45	8	**81.8%**	29,077	13,007	**63.0%**	**0.007**
Total	128	17(13.3%)	**91.0%**	89,483	47,168(52.7%)	**80.5%**	

SLNM = Sentinel Lymph Node Mapping, SEER= Surveillance, Epidemiology and End results.
Median Follow-up = 83 months, minimal follow up = 60 months. * Pts lost to follow up were excluded from the 5-year disease specific survival analysis

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Comparing the Clinical and Economic Impact of Laparoscopic Versus Open Liver Resection T. Vanounou,* J. Steel, T. Nguyen, S. Cho, D.A. Geller, T.C. Gamblin. *UPMC, Pittsburgh, PA.*

BACKGROUND: While the safety and feasibility of laparoscopic hepatectomy has clearly been established, it has not gained wide spread acceptance and remains a subject of controversy. Central to the debate is whether the comparative clinical superiority of the laparoscopic approach justifies its increased technical complexity and whether it carries any economic benefit compared to open liver surgery. OBJECTIVE: Evaluate the clinical and economic equivalence or superiority of laparoscopic versus open left lateral sectionectomy (LLS) within a tertiary referral center well versed in laparoscopic hepatectomy. METHODS: Between May 2002 and July 2008, 44 laparoscopic LLS were performed for both benign and malignant lesions with or without a hand-port. Clinical and economic parameters were compared with a contemporaneous group of open LLS. Deviation-Based Cost Modeling (DBCM) was utilized to compare the combined clinical and economic impact of the two approaches. RESULTS: The laparoscopic approach compared favorably to the open approach from both a clinical and economic standpoint. While median length of stay was shortened by 2 days in the laparoscopic group (3 vs. 5 days respectively, $p<0.0001$), the postoperative course was similar across both approaches with 84% and 83% of patients undergoing laparoscopic and open LLS respectively having an uncomplicated postoperative course according to DBCM analysis. Groups differed significantly in the ratio of benign versus malignant disease addressed with a greater proportion of open resections done for malignant disease (Chi-Square=11.2, $p<0.001$). The economic impact of the laparoscopic approach was noteworthy, but not statistically significant($p=0.06$), across all deviation levels with a weighted-average median cost savings of $2,929.81 compared to open LLS. CONCLUSION: Our study has not only affirmed the safety and clinical benefit of the laparoscopic approach but also demonstrated a fiscally important cost advantage for the minimally invasive approach thereby corroborating that laparoscopic hepatectomy fulfills the clinical and economic promises of minimally invasive surgery and should emerge as the standard approach for LLS in the future.

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Oncological outcomes following TEMS for rectal cancer

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Introduction Transanal Endoscopic Microsurgery (TEMS) has become increasingly popular for managing benign rectal lesions amenable to local excision. Whilst TME excision is the accepted oncological operative approach it carries risks of mortality and morbidity. The object of this study was to assess the long term outcome following TEMS excision for adenocarcinoma. Method Analysis was performed of a prospectively maintained unit database consisting of all TEMS procedures between 1997 and 2007. Patients with histology positive for adenocarcinoma were identified and analysed to establish outcome, recurrence of disease and mortality. Results 218 patients underwent TEMS procedures,80 of whom had histology positive for adenocarcinoma. 49(61%) were male, 31(39%) female and mean age at operation was 73 years(43-92). Histology was graded as Tis 17(22%), T0 1(1%), T1 27(34%), T2 27(34%) and T3 8(10%). 18(23%) patients encountered post operative complications, 16 post operative bleeding, one a CVA and one a MI. 26 patients died during follow up, 6(23%) related to disease, 3(12%) with disease but of other causes and 17(65%) disease free. 8(10%) underwent pre operative radiotherapy (Tis1, T26, T31), all remain disease free at present, 16(20%) underwent post operative radiotherapy (Tis1, T2 12, T3 3), 5 have recorded recurrence, 2 of whom died of disease. Subdivision for stage demonstrated recurrence rates for Tis, T1, T2, and T3 disease of 6%, 7%, 19% and 63% respectively. Mean survival following TEMS was 45 months (1-111). T stage (P≤0.05) and age at operation (P≤0.05) statistically correlated for death. Of the surviving 54 patients, median follow up is 40 months(2-129), 4(7%) have recorded recurrence(Tis 1, T2 1, T3 2). Conclusion TEMS in selective cases provides a safe alternative to TME in high risk surgical cases for Tis, T1 and T2 rectal cancers, with low morbidity and disease related mortality. Pre operative radiotherapy appears effective in preventing recurrence compared to post operative treatment. A high percentage of those whom underwent TEMS in this cohort of patients remain disease free. Whilst these numbers are limited the future role of TEMS for early rectal cancers is worthy of further assessment.

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Barriers to Surgical Therapy for Pancreatic Cancer

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Introduction: Recent data indicate that not all patients with potentially resectable pancreatic cancer undergo surgical therapy. The specific causes for the underutilization of surgical therapy is unclear; the identification of barriers to surgical therapy may allow for intervention and increase the surgical treatment of resectable pancreatic cancer. Methods: Using the California (CA) Cancer Registry, we identified all CA residents diagnosed with invasive pancreatic adenocarcinoma between 1994 and 2004 (N=26,518) who had radiologic Stage I/IIA tumors (N=3,661). Factors potentially impacting delivery of curative-intent surgical therapy including age, gender, geographic residence (urban vs. rural), time period of treatment, race, and socio-economic status (SES) were analyzed. Univariate analysis was performed by Chi-squared analysis and Hazard ratios, as appropriate. Results: Among 3,661 patients with Stage I/IIA tumors, 1,169 (31.9%) underwent resection with curative intent while 2,492 (68.1%) did not. The delivery of surgical therapy in this cohort was equivalent among time periods. Younger patients were more likely to undergo surgical therapy – 49.5% of patients <60 years (365/737) compared to 21.7% of patients >70 (447/1609). Only Black race was associated with a decreased used of surgical therapy (26% vs. 32.4%; p<0.034). SES demonstrated a linear relationship to receipt of surgical therapy – 29.1% of patients in the lowest SES quintile (139/478) compared to 36.8% of patients in the highest SES quintile (310/842) (HR 1.46; CI 1.27-1.69). Patients from rural (<2500 residents) and small towns (2500-10,000 residents) were just as likely as urban residents to undergo surgical therapy. Among patients with localized pancreatic cancer that did not undergo surgical therapy, 1,459 (58.4%) received chemotherapy and/or radiotherapy. Conclusions: Significant barriers based on age, race and SES (but not geographic residence) prevent the appropriate delivery of surgical therapy for Stage I/IIA pancreatic cancer. The administration of chemotherapy/radiation therapy in patients who did not undergo surgery suggests a specific bias against surgical resection rather than a bias against therapeutic intervention in general.

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Local Excision (LE) after Preoperative Chemoradiation (CXRT) for T3 Rectal Cancer Results in an Equivalent Outcome to Total Mesorectal Excision (TME) in Selected Patients

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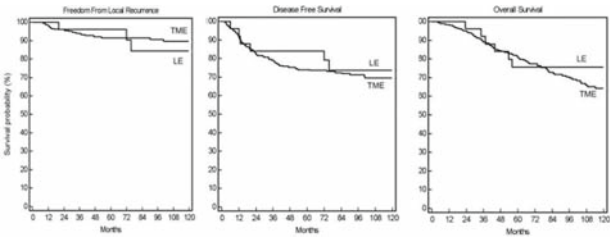
BACKGROUND: Standard therapy for T3 rectal cancer involves pre- or post-operative CXRT and surgical resection consisting of proctectomy with TME. We have previously reported on a group of patients with prohibitive comorbidity or who refused to undergo radical surgery and were offered full-thickness LE as an alternative treatment. No difference in outcome was observed between patients who underwent LE versus TME at nearly 4 years of follow-up. The purpose of the present study is to compare the local recurrence (LR), disease-free survival (DFS) and overall survival (OS) in a similar group of patients after nearly 8 years of follow-up. METHODS: A retrospective review was performed of patients who underwent preoperative CXRT followed by surgery for T3 rectal cancer. Kaplan-Meier curves were created to compare LR, DFS and OS between groups. RESULTS: From 01/1990 through 06/2002, 25 patients with T3 rectal cancer underwent preoperative CXRT followed by LE [Kraske (n=4) or transanal excision (n=21)]. A control group of 473 patients underwent preoperative CXRT followed by TME [abdominoperineal resection (n=141) or low anterior resection (n=332)] from 12/1989 through 07/2004. Median follow-up was 93 months for the LE group and 59 months for the TME group. In the LE group, 14 patients (56%) had a complete response to CXRT, 7 (28%) had microscopic residual disease, and 4 (16%) had gross residual disease. Three LE patients developed LR at 20, 72, and 76 months. Two of these patients underwent salvage surgery and currently have no evidence of disease. The other patient was initially lost to follow-up and subsequently developed simultaneous LR and metastatic disease. There was no significant difference between the 10-year actuarial LR rate for the LE group compared to the TME group (12% versus 8%; p=0.68), and no significant difference in DFS or OS between groups (p=0.64 and p=0.67 respectively; Figure 1). CONCLUSIONS: In selected patients who undergo preoperative CXRT for T3 rectal cancer, full-thickness LE offers comparable local control, DFS and OS to that achieved with proctectomy and TME.



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Characteristics of relapse after curative resection for T1 colorectal cancer: is the surveillance after initial colorectal surgery necessary?

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INTRODUCTION: The aim of this multicenter study was to clarify the characteristics of relapse after curative resection for T1 colorectal cancer and to establish the optimal surveillance schedule. METHODS: We enrolled 798 consecutive patients with curative resection for T1 colorectal cancer at the 14 hospitals between 1991 and 1996. The association between the relapse and various clinicopathologic features were analyzed. The relapse sites and the time to relapse were also evaluated. RESULTS: The rate of lymph node metastasis in patients with T1 colorectal cancer was 9.6% (75/798). Eighteen patients out of 798 (2.3%) developed relapse. Among various parameters, histologic grade (2.1% in well or moderately differentiated adenocarcinoma versus 33.3% in poorly differentiated or mucinous adenocarcinoma, p = 0.0006), location (1.5% in colon versus 4.2% in rectum), lymph node metastasis (1.3% versus 10.7%,

p<0.0001), and venous invasion (1.5% versus 6.6%, p<0.0001) were risk factors for relapse. The logistic regression analysis revealed that the lymph node metastasis was an independent risk factor for relapse after curative resection for T1 colorectal cancer (p<0.0001). The median time to relapse after colorectal surgery was 1.9 (0.3-4.4) years. Time to relapse in patients with nodal involvement was earlier than that without nodal involvement, although there was no statistically significant difference. The patients without lymph node metastasis did not recur within one year after initial surgery. The first sites of relapse were liver (7 cases), lung (4 cases), local (2 cases), anastomosis (1 case), and others (7 cases). CONCLUSIONS: In patients with T1 colorectal cancer, surveillance after curative resection may be necessary in those with lymph node metastasis or in those with poorly differentiated or mucinous adenocarcinoma. One year may be appropriate for the duration between the initial surgery and the first surveillance in patients with T1 colorectal cancer without nodal involvement. A randomized controlled study will be necessary to validate the usefulness of surveillance after curative resection for T1 colorectal cancer.

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The Impact of Breast MRI on Surgical Decision-Making: Are Patients at Risk for Mastectomy? K. Pettit,* M.E. Swatske, R.L. Aft, W.E. Gillanders, T.J. Eberlein, J.A. Margenthaler. *Surgery, Washington University School of Medicine, St. Louis, MO.*

INTRODUCTION: The role of breast MRI for evaluation of extent of disease in patients with breast cancer remains controversial. We sought to determine whether breast MRI affects multidisciplinary treatment planning and if it leads to increased rates of mastectomy. METHODS: A retrospective review was conducted of 465 consecutive patients who were treated for breast cancer at our institution between January 2005 and May 2008 who also underwent breast MRI to evaluate extent of disease. Analysis included number of patients requiring second-look imaging, number and result of additional biopsies, impact of MRI on treatment planning, and correlation of MRI findings with final pathology. RESULTS: Of 465 patients, 52 (11%) had ductal carcinoma in situ, 276 (60%) had invasive ductal cancer, 58 (12%) had invasive lobular cancer, and 79 (17%) had mixed/other invasive cancers. Overall, 197 patients (42%) had at least one additional finding on MRI, and 159 (34%) required additional imaging. Treatment planning was altered in 104 of the 465 (22%) patients; treatment changes for the 104 patients included 9 (9%) who were given neoadjuvant chemotherapy prior to successful BCT, 37 (35%) who were given neoadjuvant chemotherapy prior to mastectomy, and 13 (13%) who had a contralateral cancer identified. The remaining 45 (43%) patients were those who were initially felt to be good candidates for BCT but proceeded to mastectomy based on MRI findings. Of these 45, 8 (18%) had pre-mastectomy biopsy of the additional MRI lesions confirming multicentricity. Of 37 patients who did not have a biopsy of the MRI lesion, 34 (92%) had unicentric disease on final pathology, consistent with routine imaging. Overall, the rate of mastectomy in the study population was 41% (191 of 465), which was significantly increased compared to patients who did not undergo MRI during the same time period (32%, p<0.05). CONCLUSION: Breast MRI alters the treatment planning for a significant number of patients with newly-diagnosed breast cancer. Mastectomy rates are increased when MRI results alone direct surgical planning. Biopsy of MRI-identified lesions should be performed to avoid overtreatment.

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Evaluation of proposed candidate genetic variants in a west of Ireland breast cancer cohort N. McInerney,[1]* N. Miller,[1] A. Rowan,[2] G. Colleran,[1] C. Curran,[1] E. Sawyer,[2] I.P. Tomlinson,[2] M.J. Kerin.[1] *1. Surgery, National University of Ireland Galway, Galway, Ireland; 2. Cancer Research UK, London, United Kingdom.*

Background Positive family history is the most important risk factor in breast cancer predisposition. Following the breakthrough discovery of BRCA 1 and 2, further studies have failed to identify other high penetrance variants, leading to a new model of breast cancer susceptibility. The relatively homogeneity of the west of Ireland population is ideally suited to the study of proposed moderate and low susceptibility variants. Aim To ascertain what contribution proposed moderate and low penetrance variants make in breast cancer predisposition. Methods A cohort of 990 breast cancer patients and 1016 matched non-cancer controls were genotyped for 23 candidate single nucleotide polymorphisms (SNPs) previously shown to be significant in prostate, colorectal and breast cancer. Mutations in the suggested susceptibility genes CHEK2, BRIP1 and PALB2 were interrogated in 192 high risk patients using genescan analysis and direct sequencing. Results This study shows the association between SNPs within FGFR2, TNRC9 and also at 8q24.21 and sporadic breast cancer in a west of Ireland cohort. The absence of breast cancer risk with other variants associated with other cancers suggests that breast, prostate and colorectal susceptibility alleles are site specific. Known mutations in CHEK2 and BRIP1 were identified in patients with high genetic risk. However 5 variants in PALB2 were not evident. Conclusion Approximately 75% of familial breast cancer remains unexplained. We have identied moderate and low penetrance variants which may have implications for clinical practice as our knowledge of these variants expands. Our findings contribute to a better understanding of inherited breast cancer risk while helping to optimise future screening, therapeutic and prophylactic programs.

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Postoperative Antibiotics and Infection Rates in Breast Surgery Patients A.D. Throckmorton,* J.C. Boughey, S.Y. Boostrom, A.C. Holifield, M.M. Stobbs, L.M. Baddour, A.C. Degnim. *Mayo Clinic, Rochester, MN.*

Background: In many centers, a single preoperative dose of intravenous antibiotics is standard of care for breast and axillary procedures. However, some surgeons prescribe oral postoperative prophylaxis for all patients with drains to prevent infection despite lack of proven efficacy. Methods: Retrospective review of medical charts from patients with breast/axillary operations between 07/2004 and 06/2006. Data were collected on patient demographics, type of procedure, and use of antibiotics for prophylaxis. Surgical site infection (SSI) was defined using CDC criteria, including patients prescribed antibiotics for concern of infection. Fisher's exact test was used to compare SSI rates. Results: Forty-seven of 391 patients did not receive preoperative prophylaxis and were excluded, leaving 344 patients with 437 surgical sites who received either preoperative or both preoperative and postoperative antibiotic prophylaxis for analysis. Sixty-seven procedures involved reconstruction with expander/implant and 5 with autologous tissue. Overall, the SSI rate was 8.5 % (37/437 surgical sites). Eighty-four patients (24%) with 125 surgical sites were given both preoperative and postoperative prophylactic antibiotics. Indications for postoperative prophylaxis included reconstruction (43), neoadjuvant chemotherapy (2), diabetes mellitus (4), tobacco use (3), corticosteroid-dependence (4), initiation prior to surgery for other active infectious diseases with continuation through the postoperative period (5) and surgeon's discretion (23). The SSI rates did not differ statistically (p=0.97) for the group that did (8.8%, 95% CI 0.044-0.15, 11/125 surgical sites,) and did not (8.3%, 95% CI 0.055-0.12, 26/312) receive postoperative antibiotic prophylaxis. No antibiotic complications were attributed to preoperative prophylaxis (0/260); in contrast, 5 (6%, 5/84) adverse events were due to postoperative prophylaxis. Conclusions: In this retrospective review, there was no SSI reduction among those who received postoperative antibiotic prophylaxis. Recognizing the potential adverse events associated with antibiotic use, further evaluation of this practice is needed.

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The Effect Of Previous Hormone Replacement Therapy On Post-Menopausal Symptoms In Hormone Receptor-Positive Breast Cancer Patients Treated With Anti-Estrogen Therapy A.B. Chagpar,[1]* K.M. McMasters,[1] J. Lewis,[2] M.J. Edwards.[2] *1. Surgery, University of Louisville, Louisville, KY; 2. University of Cincinnati, Cincinnati, OH.*

Introduction: Some patients treated with hormone replacement therapy (HRT) will develop hormone receptor positive (HR+) breast cancer, and will subsequently be treated with anti-estrogen (AE) therapy. The purpose of this study was to determine whether previous HRT use affected post-menopausal symptoms when treated with AE therapy for invasive breast cancer. Methods: The North American Fareston versus Tamoxifen Adjuvant Trial is an investigator initiated multicenter trial of HR+ breast cancer patients who were randomized to receive either tamoxifen or toremifene adjuvant therapy. History of HRT and symptoms while on AE therapy were prospectively collected. Results: Of the 1709 patients randomized in this study, data regarding HRT use was collected in 783 (45.8%) patients. Of these patients, 446 (57.0%) reported a prior use of HRT. HRT users and non-users were evenly distributed between the two AE treatment arms, with 51.6% of HRT users and 49.6% of non-HRT

users being randomized to the tamoxifen arm, p=0.577. HRT users tended to be younger (median patient age 65 vs. 71 years, p<0.001), with a lower body mass index (BMI: 26.6 vs. 28.0, p=0.012). With a median follow-up of 59 months, previous HRT users had a higher incidence of hot flashes (54.3% vs. 32.5%, p<0.001), vaginal dryness (17.1% vs. 3.2%), and night sweats (22.0% vs. 9.2%, p<0.001) when on AE therapy. On multivariate analysis, controlling for age and BMI, previous HRT use remained a significant predictor of hot flashes (OR: 2.085, 95% CI: 1.455-2.989, p<0.001), vaginal dryness (OR: 4.953, 95% CI: 2.303-10.653, p<0.001), and night sweats (OR: 2.665, 95% CI: 1.580-4.495, p<0.001). In addition, the development of post-menopausal symptoms was associated with a longer duration of HRT use: hot flashes (mean 7.0 vs. 4.7 yrs, p<0.001), vaginal dryness (mean 8.4 vs. 5.4 yrs, p<0.001), and night sweats (mean 8.6 vs. 5.2 yrs, p<0.001). Conclusion: Prior HRT use is associated with an increased incidence of hot flashes, vaginal dryness and night sweats in breast cancer patients treated with AE therapy.

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Second Primary Lung Cancer Associated with Breast Conservation Therapy N.R. Poulin,* E. Feliberti. *Dept of Surgery, Eastern Virginia Medical School, Norfolk, VA.*

Introduction: Radiation therapy provides breast conservation therapy (BCT) equivalent local control and survival as mastectomy in the treatment of breast cancer. Its use, however, predisposes patients to the development of secondary cancers. We examined the risk associated with radiation therapy in breast cancer treatment of developing a second primary lung cancer. Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) program of the U.S. National Cancer Institute from 1973 to 2005 was examined. Search was limited to women with nonmetastatic breast cancer who were later diagnosed with lung cancer. Standardized incident ratios (SIR) were calculated to determine the risk of second primary lung cancers in those who did and did not receive radiation. Results: During the time period, 395,510 women were diagnosed with breast cancer, of which 5,406 developed a second primary lung cancer (1.4%). Radiation therapy was associated with an increased risk of lung cancer with lumpectomy and with mastectomy at 10-14 years after treatment (SIR 1.21 and 1.42, respectively), while no increased risk was observed with lumpectomy or mastectomy alone (SIR 0.9 and 0.93, respectively). This increased risk associated with BCT was observed at 10-14 years for localized and regional breast cancer (SIR 1.24 and 1.45, respectively). Women younger than 50 years old treated with radiation had a significantly higher risk of developing a second primary lung cancer, with the greatest risk seen in women aged 25-29 and 30-34 years old (SIR 9.8 and 4.4, respectively). No increased risk was noted in patients aged 50 and older who received radiation. Conclusions: Radiation as part of BCT is associated with an increased risk of a second primary lung cancer starting at 10 years after treatment. This risk is age-dependent, affecting patients younger than 50 years old, and progressively escalates as age decreases.

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National Quality Measures for Breast Centers: A Robust Quality Tool C.S. Kaufman,[1]* L. Shockney,[2] B. Rabinowitz,[3] C. Beard,[4] C. Coleman,[5] J. Landercasper,[6] J. Askew, Jr.,[7] D. Wiggins,[8] A. Quality Initiative Committee.[8] *1. University of Washington, Bellingham Breast Center, Bellingham, WA; 2. Johns Hopkins Avon Foundation Breast Center, Baltimore, MD; 3. Meridian Health/Ocean Medical Center, Brick, NJ; 4. Baptist Hospital for Women, Memphis, TN; 5. Coleman Breast Center Consultation Services, Tiburon, CA; 6. Gundersen Lutheran Surgery Clinic, LaCrosse, WI; 7. Houston NW Hospital Breast Center, Houston, TX; 8. National Consortium of Breast Centers, Inc., Warsaw, IN.*

Introduction: Measuring quality of care is of primary interest to patients, clinicians and payers. The National Consortium of Breast Centers (NCBC) has created a unique method to examine the quality of interdisciplinary breast care provided by breast centers across the country. Methods: In 2005 the NCBC Quality Initiative Committee formulated their initial series of 36 measurements of breast center quality, eventually called the National Quality Measures for Breast Centers (NQMBC™). Measures were derived from published literature as well as expert opinion. An interactive website was created to receive measurement data from individual breast centers and to provide each breast center with comparison reports. Breast centers submit their answers to measures using data they collect over a single month on consecutive patients. Centers can compare their results with centers of similar size and demographic or compare themselves to all centers who supplied answers for that measurement. New data may be submitted twice yearly. Serially submitted data allow centers to compare themselves over time. Random audits confirm accuracy of submitted data. Early results on several initial questions are reported here. Results: Over 200 centers are submitting data to the NQMBC™ via the Internet without charge. These questions provide insight as to timeliness of care provided by radiologists, surgeons and pathologists. Results are expressed as the mean average including 25th and 75th percentiles for each metric. This sample of seven questions includes data from over 30,000 patients, creating a powerful database. In addition, comparison results are available every six months, recognizing that benchmarks may change over time. (See table). Conclusions: A real-time web-based quality program allows breast center input with immediate comparisons to other centers, and provides results serially over time. Data may be used by centers to recognize high quality care they provide or to identify areas which need improvement. Results of some initial parameters demonstrate the power of web-based evaluation of data from thousands of patients.

Some Results from the National Quality Measures for Breast Centers™

Discipline	Quality Question Number	Question Description	Number patients included in results	Aggregate mean (25th, 75th percentile)	2005 results (25th, 75th percentile)	2007 results (25th, 75th percentile)	2008 results (25th, 75th percentile)
Radiologist	#1	Time between screening mammogram and diagnostic mammogram (days)	6,500	6.5 (4, 10.5)	5.9 (4, 11)	6 (4.2, 10.1)	5.1 (3.25, 8.5)
Radiologist	#4	Time between diagnostic mammogram and needle biopsy (days)	6,000	6 (3.9, 9)	5.6 (3.1, 8.8)	7 (4, 9)	4 (2.8, 4.9)
Radiologist / Surgeon	#6	Needle/core biopsy as method of cancer diagnosis (percent)	5,500	90% (78%, 98%)	91% (74%, 96%)	91% (79%, 99%)	92% (88%, 99%)
Surgeon	#3	Time between diagnostic mammogram and open surgical biopsy (days)	4,400	13.9 (8, 19.8)	16.5 (10.5, 21)	12.6 (6.8, 18)	14 (10, 17.8)
Surgeon	#5	Time between needle biopsy and initial cancer surgery (days)	5,400	14 (11, 19.5)	14 (9.2, 19.4)	15.3 (13, 19.1)	14 (11.5, 19.3)
Pathologist	#8	Time between surgical biopsy and pathology results (days)	1,700	2 (1.7, 3)	2.8 (2, 3)	2 (1.2, 3)	3.2 (3, 3.2)
Pathologist	#11	Percent closest surgical margin noted and measured in mm, (percent)	2,000	100% (96.5%, 100%)	100 (100, 100)	100 (94.2, 100)	100 (100, 100)

Data obtained as of August 31, 2008.

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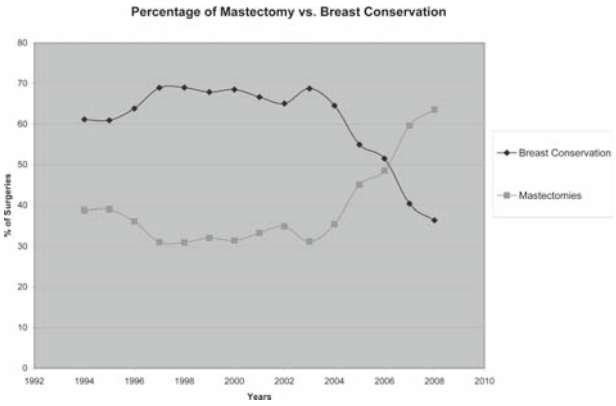
Are mastectomies on the rise? A 13 year trend analysis of the selection of mastectomy vs. Breast Conservation Therapy in 5865 patients K.P. McGuire,* A. Santillan, P. Kaur, D. Ramos, J. Parbhoo, M. Mathias, C. Shamehdi, M. Davis, T. Meade, C. Cox. *Moffitt Cancer Center, Tampa, FL.*

Introduction: The equivalency of survival between patients undergoing mastectomy and breast conservation therapy (BCT) has long been established, resulting in two decades of predominant BCT. Recently, surgeons recognize a trend toward increasing mastectomy. Trends in mastectomy and BCT were reviewed confirming this perception in the surgical treatment of breast cancer. This report attempts to evaluate the factors that influence patient decisions to choose surgical therapies. Methods: 5865 patients undergoing either mastectomy or BCT for invasive and in-situ breast cancer were identified in retrospective review of a prospectively accrued breast cancer database between the years of 1994 and 2007. Univariate and multivariate logistic regression analysis were used to estimate the odds ratio (OR) of the association between mastectomy and patients' clinicopathologic characteristics. Results: Of the 5865 patients, 3736 underwent BCT, while 2129 underwent mastectomy. Mastectomy rates during the periods of 1994-1998, 1999-2003, and 2004-2007 were 33%, 33%, and 44%, respectively (p<0.01). Plastic reconstruction rates for mastectomy during the same time periods were 34%, 12%, and 12% respectively (p<0.01). On logistic regression analysis, gender, age < 40 years, plastic reconstruction, increase tumor size, and lymphovascular invasion were significant independent predictors of mastectomy. Using the period of 1994-1998 as the reference group, mastectomy rate rose strongly from 1999-2003(OR 1.2) and from 2004-2007(OR 1.8). Conclusions: The perception of an increasing treatment choice towards mastectomy has been confirmed at this institution. Possible reasons for this change may be a younger population with higher lifetime risk, fear of recurrence, higher stage disease, more biologically aggressive or diffuse tumors. Patient preference, fear of genetic or recurrence risk

and "intangible" factors appear to be shifting decisions toward mastectomy and away from breast conservation.



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Breast cancer- Is she really at high risk? A validation study of the Pedigree Assessment Tool (PAT) P. Teller,[1]* S. Gabram,[1] A. Zwaagstra,[1] C. Stanislaw,[3] R. Iyengar,[1] V.L. Green,[4] K.F. Hoskins.[2] *1. Surgical Oncology, Emory University, Atlanta, GA; 2. OSF Saint Anthony Center for Cancer Care, Rockford, IL; 3. Emory University Department of Human Genetics, Atlanta, GA; 4. Emory University Department of Obstetrics & Gynecology, Atlanta, GA.*

INTRODUCTION: The lifetime risk of developing breast cancer in patients with genetic mutations is as high as 80%. The Pedigree Assessment Tool (PAT) is a simple point scoring system designed to aid surgeons in identifying patients at high risk for hereditary breast cancer syndromes. This validation study compares the PAT to existing BRCA gene mutation probability models in predicting suitability for genetic referral. METHODS: A retrospective chart review was conducted at two institutions. All subjects underwent genetic counseling and BRCA testing from 2001 to 2008. Familial risk factors for breast cancer plus BRCA test results were collected. PAT score and BRCA mutation probabilities were calculated (utilizing both the Myriad and Penn II models). Comparisons were made between models in their ability to discriminate patients appropriate for genetic evaluation based on accuracy in predicting a positive test result. RESULTS: Records evaluated represent 460 families. BRCA testing revealed 124 mutation positive families and 336 negative. The c-statistic analysis provided statistical comparison of the discriminating ability of the three models to correctly assign families to mutation (+) and mutation (-) cohorts. By c-statistic, the PAT performed as well as the Myriad and Penn models. Using threshold value of PAT score ≥ 8 and mutation probability ≥ 10% (Myriad and Penn) to assign families to the mutation (+) vs. mutation (-) cohorts, sensitivity, specificity, positive predictive (PV+) and negative predictive (PV-) values were calculated for each model. The PAT was statistically more sensitive than the Myriad model although less specific. No significant difference exists between the PAT and Penn models. PV+ and PV- were comparable for all models. CONCLUSION: The PAT is statistically superior to the Myriad model for use as a screening tool to identify women appropriate for genetic referral by virtue of high risk for BRCA mutation. It is also better suited for this purpose than the Penn model given its simplicity. This data supports the use of the PAT as a component of breast cancer risk screening and further study with this model is warranted.

Comparison of PAT, Myriad and Penn Mutation Prediction Models

	c-statistic	Sensitivity*	Specificity*	Positive predictive value (PV+)	Negative predictive value (PV-)
PAT	0.690 ±0.004	0.952 ±0.038	0.190 ±0.042	0.303 ±0.046	0.914 ±0.066
Myriad	0.664 ±0.005	0.839 ±0.065	0.381 ±0.052	0.333 ±0.052	0.865 ±0.055
Penn	0.706 ±0.004	0.911 ±0.050	0.145 ±0.038	0.289 ±0.045	0.824 ±0.099
p-value PAT v. Myriad	0.213	0.037	< 0.0001	0.384	0.293
p-value PAT v. Penn	0.436	0.293	0.119	0.695	0.129

*Probability threshold: PAT ≥ 8, Myriad and Penn ≥ 10%. X2 test used to determine p-value. Statistical significant p £ 0.05

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Desmoids - A revelation in biology and treatment W.P. Francis,[1]* D. Zippel,[3] L. Mack,[1] L.D. DiFrancesco,[2] E. Kurien,[2] N. Schachar,[2] W.T. Temple.[1] *1. Surgical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada; 2. University of Calgary, Calgary, AB, Canada; 3. Chaim Sheba Medical Center, Tel Hashomer, Israel.*

Introduction Using a preoperative neoadjuvant chemoradiation protocol, followed by complete excision, we have achieved local control rates exceeding that found in most large series. Altering this approach, with an attempt to determine tumor biology, has allowed equally achievable results. Methods From October 1990 through May 2008 resectable desmoids were initially treated with a preoperative protocol using Adriamycin 30mg x 3 days continuous infusion followed 3000cGy of radiation (300cGy fractions over 10 days). Resection was performed 4-6 weeks later. After 2001, all patients were initially offered Tamoxifen 120mg/day and Celebrex 400mg/day for 1 year. Patients who progressed on Tamox/Celeb were treated with protocol and those with stabilization or regression were observed. Patient demographics, tumor size, history of previous recurrences and follow-up status were recorded prospectively Results Fifty-two patients made up the study population. There were 40 females and 12 males with a mean follow-up of 45 months (Range 0.2-149.5). Mean age at diagnosis was 33 years (Range 13-82). Forty four patients presented with primary tumors and 8 presented with recurrent disease. Mean tumor size was 7cm (range, 2-30cm). Thirty-nine patients had surgical resection and 13 were observed. Thirty patients underwent the neoadjuvant protocol. Tamoxifen and Celebrex were used in 16 patients, 6 had stabilization in growth, 1 had a 50% reduction in the size of the tumor, there was 1 complete regression and 8 progressed on therapy. This resulted in a 50% response rate. Of the patients who had resectable disease Tamoxifen and Celebrex obviated surgery in 30%. Overall 13% (5) of patients developed a recurrence. There were 3 recurrences among the protocol group for a local control rate of 90%. Conclusion Using the growth characteristics to naturally select the tumors that mandates an aggressive approach is important before deciding therapeutic options. Although our neoadjuvant protocol demonstrates the best results to date in eradication of disease, an initial conservative approach is reasonable to determine who would most benefit from surgery.

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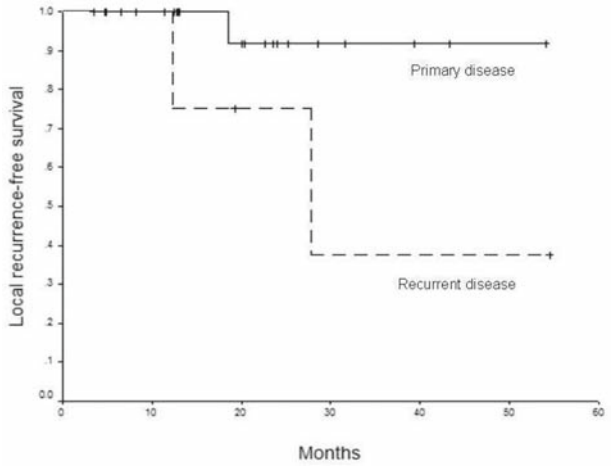
Proton Beam, Intensity Modulated, and/or Intra-Operative Radiation Therapy Combined with Aggressive Anterior Surgical Resection for Retroperitoneal and Pelvic Sarcomas U.M. Maduekwe,* T.F. DeLaney, Y. Chen, W.K. Kobayashi, A.E. Rosenberg, G.P. Nielsen, D.V. Sahani, E. Choy, D.C. Harmon, S.S. Yoon. *Surgery, Massachusetts General Hospital, Boston, MA.*

Introduction: Local recurrence for retroperitoneal and pelvic sarcomas (RPS) following surgery alone is common and the role of radiation therapy is controversial. We sought to reduce local recurrence using a novel, coordinated strategy of radiation and surgery. Methods: Proton beam (PBRT) and/or intensity modulated radiation therapy (IMRT) were delivered to improve tumor target coverage and spare selected adjacent organs/structures. Aggressive surgical resection was performed to obtain a negative anterior margin. Intra-operative radiation therapy (IORT) was delivered for a close or positive posterior margin. Results: 27 pts (median age 57) were treated with this strategy. 19 pts had primary tumors and 8 had recurrent tumors. Tumors were large (median size 10 cm), primarily liposarcomas and leiomyosarcomas (74%), and mostly intermediate- or high-grade (80%). PBRT was given to 10 pts, IMRT to 10 pts, and both PBRT and IMRT to 7 pts to a median dose of 50 Gy. Radiation was preferably given preoperatively (78%). Surgical resection included up to 5 adjacent organs/structures, most commonly colon (n=8) and kidney (n=7). Margins were positive, usually posteriorly, in 15 pts (56%). IORT was delivered to the posterior margin in 12 pts to a median dose of 11.8 Gy. Surgery-related complications occurred in 8 pts (30%). Radiation-related complications occurred in 4 pts (15%) (ureteral stricture, delayed bleeding, and 2 late infections). After a median follow-up of 21 months, 1 pt (5%) with primary disease had a local recurrence, 2 pts (25%) with recurrent disease had a local recurrence (see Figure), and 5 pts (19%) had distant recurrences. Conclusions: Aggressive resection of RPS can result in a negative anterior margin. PBRT, IMRT, and/or IORT allow delivery of adequate radiation doses to the posterior margin to control microscopic residual disease with acceptable morbidity. This treatment strategy may reduce local recurrence, especially in patients with primary disease.



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Complete pathologic response to neoadjuvant chemoradiation is the only predictor of survival in patients with esophageal cancer

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Introduction: Esophageal cancer remains a malignancy with high morbidity and mortality despite improvements in diagnosis, staging, chemo and radiotherapy and surgery. Neoadjuvant therapy (NT) with complete pathologic response (pCR) is achieved in 30% of patients. We examined the magnitude of response from NT and degree of benefit with pCR. Methods: Using a comprehensive esophageal cancer database we identified patients who underwent esophagectomy between 1994 and 2008. Only adenocarcinoma and squamous carcinomas were included in data analysis. Clinical and pathologic data were compared using Fisher's exact and chi-square tests when appropriate while Kaplan Meier estimates were used for survival analysis. Results: We identified 369 patients (320 adenocarcinomas and 49 squamous cell carcinomas) with a mean age of 64 +/- 10 years and mean follow-up 22 +/- 22 months. NT was used in 252 (68%) patients while 117 (32%) patients went straight to surgery (SS). There were 83 (33%) patients exhibiting a pCR, 122 (48%) a partial response (pPR), and 47 (19%) non-responders (NR). The rate of R1 resections was significantly lower in the pCR 0% compared to the pPR 7.6% (p=0.012), non-responders 11% (p=0.008) and 18% in SS group (p<0.001). There were 96 (26%) recurrences with a median time to recurrence of 8.7 months (1.5-68 months). Tumors exhibiting a pCR had a 17.7% recurrence in the adenocarcinomas v/s 31.2% in the SS and NR (p=0.03) and no difference in the squamous carcinomas 26.7% v/s 19.2% (p=0.43). Survival analysis showed a significant difference in overall and disease free survival (DFS) at three years; pCR (82% and 67%), pPR (61% and 51%), NR (47% and 21%), and SS (57% and 42%) p=0.003 and p=0.0001 respectively. Stage specific analysis corroborated this benefit for stage II and III patients. Conclusions: Esophageal cancer patients frequently succumb to their disease. However, patients treated with neoadjuvant therapy who demonstrate a pCR have lower rates of R1 resections, lower recurrences, and improved overall survival.

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Clinical, pathological and molecular variables predictive of malignant peripheral nerve sheath tumor (MPNST) outcome

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Introduction: There is a need to devise new staging systems to aid in malignant peripheral nerve sheet tumor (MPNST) prognostication and management. Towards that goal we aimed to identify clinical, pathologic and molecular predictors of outcome in patients with/without NF-1-associated MPNST treated at a single institution. Methods: MPNST patients treated from 1986 to 2006 (n=140) were identified; 72 had NF-1 syndrome and 68 did not. A comprehensive database was constructed. 127 formalin-fixed paraffin-embedded neurofibroma or MPNST blocks were assembled in a tissue microarray; expression of a panel of molecular markers was evaluated via IHC. Univariable and multivariable analyses identified independent factors prognostic of local recurrence, distant metastasis and disease specific survival (DSS). Results: After median follow up of 91 months, DSS at 10 years was 31.6% for 87 primary disease patients, 25.9% for 26 recurrent patients, and 7.5% for 27 metastatic patients. The 5-year DSS for patients with localized tumors was 35% for NF-1 syndrome patients and 50% for sporadic patients. Tumor size ≥10 cm at time of diagnosis, partial surgical resection, and eventual metastasis development were significant negative predictors of DSS. In addition, localized tumors with a lack of S-100 immunoreactivity had a 5-fold increased risk of developing distant metastasis. Ki67, VEGF, p53, EGFR, and pMEK were all overexpressed in MPNST compared to benign neurofibromas. Expression of EGFR and nuclear p53 were associated with significantly worse disease-specific MPNST survival. Conclusions: MPSNT is a markedly metastatic and aggressive tumor, harboring a dismal prognosis. A variety of clinical, pathological, and molecular markers identified in our study in combination with findings from previous series should be considered in the development of a new staging system that can be utilized for MPNST prognostication assessment and management direction.

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Outcomes of soft tissue sarcoma surgery in the elderly G.J. Lahat,* A. Dukah, S. Lahat, B. Feig, J. Cormier, K. Hunt, P.W. Pisters, D. Lev, R.E. Pollock. *surgical oncology, MDACC, Houston, TX.*

Introduction: Reports suggest increased soft tissue sarcoma (STS) specific mortality risk in older patients. Decreased performance status, comorbidities, and disease natural history may further erode enthusiasm for STS resection. Consequently, sarcoma resections in elderly patients were evaluated to determine if age per se correlated with unfavorable surgical outcomes. Methods: Prospectively accrued data were analyzed for all primary STS patients age > 65 years (n=325) who had complete macroscopic resection at our institution from 1996-2007. Results: Multivariable analysis identified age >75 years as an adverse prognostic factor for STS specific survival (HR=2.03; p=0.002), so we compared this group (n=122) to those aged 65 to 74 years (n=203). ASA 3-4 status prevalence was comparable (>75: 60.2% vs 65-74: 51.7%; ns); STS size, location, depth, histology, and use of radiotherapy likewise did not differ between groups. However, high grade STS was more common in the elderly (65-74: 67.0% vs >75: 78.0%; p=0.04). Measures of surgical outcome; i.e., margin positivity, complication rate, and length of hospital stay were comparable, as was peri-operative mortality (65-74: 0/203 vs >75: 2/122; ns). Metastasis was more common in the elderly (65-74: 8.4% vs >75: 18.7%; p<0.01); although they had higher grade STS, they received chemotherapy less often (65-74: 33.2% vs >75: 13.8%; p<0.0001) and had shorter median STS-specific survival (65-74: 46 mo. vs >75: 36 mo; p=0.02). In contrast, local failure was more common in the younger group (65-74: 32.5% vs >75: 19.5%; p=0.001), perhaps because they lived longer without developing distant disease. Conclusions: Properly selected, elderly patients can safely undergo STS resections without adverse impact on surgical outcomes. Although their STS-specific survival was shorter, this may be due to an increased prevalence of high grade STS, increased rates of STS dissemination, and possibly less use of chemotherapy in this group. Until more efficacious systemic treatments become available, surgery in the elderly is both indicated and may remain the best means to provide potentially curative therapy.

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Predictors of Recurrence and Survival in Primary Leiomyosarcoma

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Introduction: Leiomyosarcoma (LMS) is a common type of soft tissue sarcoma (STS), however historically their outcome has been confounded by inclusion of GIST tumors. Thus, we sought to report the natural history of primary LMS patients and the predictive factors that are associated with recurrence and survival. Methods: Between July 1982 and June 2006, 377 patients with primary resectable LMS were identified from a prospective institutional database. Uterine LMS and GIST patients confirmed by pathologic review were excluded. A multivariate analysis of clinicopathologic factors for disease-specific survival (DSS) and a competing risk survival analysis was performed

to determine factors predictive for recurrence. Results: Of 377 patients with primary LMS resected, 170 (45%) presented with extremity (Ext), 168 (45%) abdominal/retroperitoneal (Abd/RP) and 39 (10%) were truncal (Tr) tumors. The median age at presentation was 57 years (18-88). Median follow-up was 50 (1-271) months. The majority of tumors were high grade (76%), deep (75%), completely resected (R0:79%,R1:15%,R2:6%) and had a median size of 6.4 cm (0.3-45 cm). Abd/RP LMS was associated with an inferior long-term DSS compared to the Ext or Tr groups (p=0.001). However, only high grade and size were significant independent predictors of DSS by multivariate analysis (Table 1). Overall, 157 patients (42%) recurred, 58% Abd/RP, 36% Ext and 6% Tr patients. The most common site of first recurrence was a distant site in 63% of patients, 25% of patients had LR only and 12% had LR + DR. Recurrence patterns varied by primary LMS site as 82% of Ext patients had DR only, 70% DR in Tr vs. 51% DR in Abd/RP patients. The significant independent predictors for LR were size, grade, Abd/RP location and completeness of resection, whereas predictors for DR were size depth and grade (Table 1). Conclusions: Abd/RP location is an important clinical parameter in LMS as DSS in Ext and Tr patients is stable long-term, whereas Abd/RP patients experience late recurrence and demise. Strikingly, grade and size are significant predictors of DSS, LR and DR. These findings may be useful for determining which primary LMS patients should undergo adjuvant therapy.

Table 1. Multivariate Analysis of Factors Associated with Local Recurrence (LR), Distant Recurrence (DR) and Disease-Specific Survival (DSS) in Primary LMS

	Factor	p value	HR (range)
LR	Margin (R1/R2) vs. R0	0.02	1.8 (1.1-3.0)
	Abd/RP Site vs. Ext	0.02	2.1 (1.1-3.9)
	Size >5cm vs. <5cm	0.03	2.2 (1.1-4.3)
	High vs. Low grade	0.02	3.4 (1.2-9.3)
DR	Size >5cm vs. <5cm	0.009	1.8 (1.2-2.8)
	Deep vs. superficial	0.03	2.1 (1.1-4.0)
	High vs. Low grade	<0.001	6.7 (2.8-16.3)
DSS	Size 5-10cm vs. <5cm	0.008	2.3 (1.2-4.1)
	Size >10cm vs. <5cm	<0.001	4.2 (2.3-7.6)
	High vs. Low grade	0.001	4.9 (1.9-12.4)

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Survival Rates in Patients (Pts) with Metastatic Gastrointestinal Stromal Tumor (GIST) Treated with Sunitinib Malate (SU) and Cytoreductive Surgery (CS) C.P. Raut,* J.A. Morgan, S. George, A.J. Wagner, J.E. Butrynski, Q. Wang, J. Manola, C.D. Fletcher, G.D. Demetri, M.M. Bertagnolli. *Dana-Farber/Brigham and Women's Cancer Center, Boston, MA.*

Introduction In pts with metastatic GIST on first-line imatinib (IM) therapy undergoing CS, response to IM at the time of surgery correlates with completeness of resection, progression-free survival (PFS), and overall survival (OS). Pts with IM-resistant metastatic GIST treated with second-line SU have a median PFS of 7mo. We report the feasibility of resection and the first survival rates in pts following CS after SU therapy. Methods Between 2003 and 2008, 50 pts underwent CS after SU therapy for multifocal metastatic GIST. Response to SU at the time of CS was categorized as objective response/stable disease (OR/SD), limited progression (LP) or generalized progression (GP). Completeness of resection was categorized as R0, R1, or R2. Results Treatment history, completeness of resection, and survival rates are in the Table. All pts were heavily pretreated; 100% received IM for a median of 18.7mo. CS was performed after a median of 6.7mo of SU. At time of CS, 10 pts (20%) had OR/SD, 22 pts (44%) had LP, and 18 pts (36%) had GP. R0/R1 resections were performed in 26 pts (52%). Six pts (12%) had stable but unresectable liver disease and R2 resections were planned from the outset. Thus, completeness of resection did not correlate with response to SU. The complication rate was 54%; there was one postoperative death. With a median postoperative follow-up of 14.7mo, median PFS was 5.0mo after surgery, 15.2mo after start of SU, and 40.7mo after diagnosis of metastatic disease. PFS was significantly worse in pts with GP (p=0.007). Median OS was 12.3mo after surgery, 20.9mo after start of SU, and 50.9mo after diagnosis of metastatic disease. Differences in OS based on response to SU did not reach statistical significance. Conclusion CS is feasible in highly selective pts within this heavily pretreated population, but R2 resections are common and complication rates are significant. The clinical relevance of the survival rates is difficult to assess due to the inherent selection bias in this series. The palliative and therapeutic benefits of CS should be weighed against pt symptoms and alternative treatment options.

Treatment History, Surgical Details, and Survival

		No. (%)	Range
Age at surgery (median)		55.1 yrs	26.6-79.9 yrs
Gender	Men	34 (68)	
Disease presentation	Primary	27 (54)	
	Metastatic	23 (46)	
Pts with surgery prior to IM		40 (80)	
Pts with surgery on IM		16 (32)	
Median (mean) length of IM therapy		18.7 mo (24.3 mo)	3.6-65.2 mo
Median (mean) length of SU therapy		6.7 mo (9.9 mo)	1.9-48.2 mo
Response to SU at time of surgery	OR/SD	10 (20)	
	LP	22 (44)	
	GP	18 (36)	
R0 or R1 resection	OR/SD	4 of 10 (40)	
	LP	14 of 22 (64)	
	GP	7 of 18 (39)	
Median PFS after surgery	OR/SD	Not achieved	
	LP	7.9 mo	95% CI 4.2-unk mo
	GP	4.1 mo	95% CI 2.0-7.5 mo
Median OS after Surgery	OR/SD	Not achieved	
	LP	18.5 mo	95% CI 15.4-21.9 mo
	GP	8.9	95% CI 3.8-14.0 mo

IM, imatinib mesylate; SU, sunitinib malate; OR/SD, objective response/stable disease; LP, limited progression; GP, generalized progression; CI, confidence interval

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Diffuse Malignant Peritoneal Mesothelioma: Prognostic Significance of Lymph-node Metastases D. Baratti,* S. Kusamura, A.D. Cabras, B. Laterza, M. Deraco. *Fondazione IRCCS Istituto Nazionale Tumori Milano, Milano, Italy.*

Improved survival has been reported for diffuse malignant peritoneal mesothelioma (DMPM) treated by cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). The significance of lymph-node involvement in this disease is poorly understood. METHODS Prospectively collected clinical data on 76 consecutive patients with DMPM undergoing cytoreduction and closed abdomen HIPEC with cisplatin and doxorubicin were reviewed. Clinically suspected lymph-nodes were submitted to pathological examination. The impact of nodal involvement on survival was assessed by multivariate analysis; 13 clinical, pathological and biological factors were tested as control variables: age, sex, performance status, histology, extent of previous surgery, prior systemic chemotherapy, extent of peritoneal involvement, completeness of cytoreduction, baseline serum CA125, mitotic count (MC), nuclear grade, cisplatin and doxorubicin dosage RESULTS For the overall series, median follow-up was 45 months (range 3-117) and 5-year overall survival (OS) 48.7%. Lymph-nodes were submitted to pathological examination in 32 patients, being positive in 11 and negative in 21. Lymph nodes were deemed as clinically negative and not assessed by pathology in 44 patients. Iliac (n=6) and ileocolic (n=3) nodes were the most common sites of tumor involvement. OS was 18.0% for pathologically positive and 82.5% for negative node patients (P=.0024). Pathologically negative (vs. positive/not assessed) nodes (hazard ratio (HR) 5.85; 95% confidence interval (CI) 1.36-25.12; P .013), epithelial subtype (HR 3.1; CI 1.26-7.16; P .0174) and MC ≤5/50 HPF (HR 6.69; CI 2.27-19.71; P .0006) were independent risk factors for increased OS. Positive nodes (vs. negative/not assessed) did not significantly correlate to OS. CONCLUSIONS Pathologically negative nodes (as compared to positive and clinically negative), along with pathological and biological features, independently correlated to increased survival following comprehensive treatment. This suggest the need of a careful node sampling when performing surgical cytoreduction.

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Pathologic Staging and Tumor Necrosis after Laparoscopic Ultrasound Guided Radiofrequency Ablation as Bridge Therapy for Orthotopic Liver Transplant in Hepatocellular Carcinoma

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Introduction:Staging of Hepatocellular Carcinoma(HCC)with imaging studies is inaccurate. In addition,the pathologic changes when Laparoscopic Ultrasound guided Radiofrequency Ablation (L-RFA) is used as the sole modality for bridge therapy prior to Orthotopic liver transplant(OLT)have not been well characterized. This study was done to establish the accuracy of intraoperative ultrasound staging (IOUS), and to better describe the histologic changes induced by L-RFA. Methods: Pathologic staging using UNOS criteria was done in explanted livers following L-RFA and OLT. A liver pathologist reported the degree of ablation induced necrosis as a % of the total tumor volume. Results: Thirty-four livers were examined.Only patients in whom the OLT was done more than 15 days after the L-RFA were included. IOUS accurately staged 62% (n=21)of the patients. In 15% (n=5), IOUS understaged the disease, and in 24% (n=8), it overstaged it. A total of 53 tumors where found in the 34 livers. Three livers had multifocal disease. Histologically,51 tumors were HCC, one was a collision tumor (HCC & cholangiocarcinoma (CCA)), and one was a CCA. Seventy-five percent(n=40) of the tumors had some ablation necrosis and 25% (n=13) had none. Of ALL the tumors,41%(n=23) had less than 50% necrosis, 16% (n=6)had necrosis between 50 and 79%, and 43% had abaltion necrosis 80% or greater. In 30% (n=16)of ALL the tumors, 100% necrosis was noted. The size,and the number of tumors influence the % of ablation necrosis (Table 1). Conclusions: Accurate staging of HCC in the setting of cirrhosis continues to be a significant challenge. It is unclear if more accurate staging will translate into better patient selection for OLT and improved survival rates. L-RFA as the sole modality, can produce complete tumor necrosis in one third of the patients, and necrosis of 50% or more in 59% of patients selected for bridge therapy.Combined therapeutic modalities are needed to increase the number of tumors in which 100% necrosis can be achieved in those patients selected for bridge therapy prior to OLT.

Ablation necrosis by tumor size and multifocality

TUMOR SIZE	% ABLATION NECROSIS
<2cm	22%
2-4 cm	72%
>4cm	53%
MULTIFOCALITY	
1 TUMOR	63%
2 TUMORS	49%
3 TUMORS	43%

Table 1.Single tumors between 2 and 4 cm. in size had the greatest percentage of ablation necrosis

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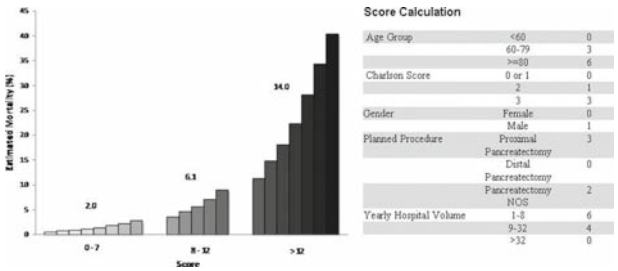
Risk Score to Predict In-Hospital Mortality after Pancreatic Resection for Cancer J.S. Hill,* Z. Zhou, J.P. Simons, S.C. Ng, T.P. McDade, G.F. Whalen, J.F. Tseng. *University of Massachusetts, Worcester, MA.*

Introduction: While pancreatic resection is being performed with lower perioperative mortality in the current era than in previous decades, these procedures continue to carry substantial risk. The relative impact of various factors affecting mortality is ill defined. An integer-based risk score generated from national data was created to estimate the risk of in-hospital mortality in patients undergoing pancreatic resection. Methods: Records with the diagnosis of pancreatic cancer were queried from the Nationwide Inpatient Sample from 1998-2006. Procedures were categorized as proximal, distal or non-specified pancreatectomies based upon ICD-9 codes. Logistic regression and bootstrap methods were used to create an integer risk score for estimating the risk of in-hospital mortality using patient demographics, comorbidities (as defined by the Charlson comorbidity score), procedure, and hospital type. A randomly selected sample of 80% of the cohort was used to create the risk score with validation of the score conducted in the remaining 20%. Results: A total of 5,715 unique patient-discharges were identified. Overall in-hospital mortality was 5.8%. Predictors utilized for the final model were age group, Charlson score, sex, type of pancreatectomy and hospital volume status (low 1-8/yr, medium 9-32/yr or high >32/yr). The coefficients from the logistic regression were converted into integer values assigned to these characteristics, and then used for calculating an additive score (Figure, right panel). Three clinically useful score groups (Low-risk [0-7 points], Medium-risk [8-12 points], and High-risk [>12 points]) were defined to stratify risk of in-hospital mortality (Figure, left panel; Mortality = 2%, 6.1% and 14% respectively; P<0.0001). There was sufficient discrimination of both the derivation set and the validation set, with c-statistics of 0.72 and 0.70, respectively. Conclusions: An integer-based risk score can be used to accurately predict in-hospital mortality after pancreatectomy, and may be useful for preoperative risk stratification and patient counseling. A risk score >12 may constitute prohibitive risk and operations in such patients should be carefully weighed.



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Proposal of New Staging in Advanced Colorectal Cancer

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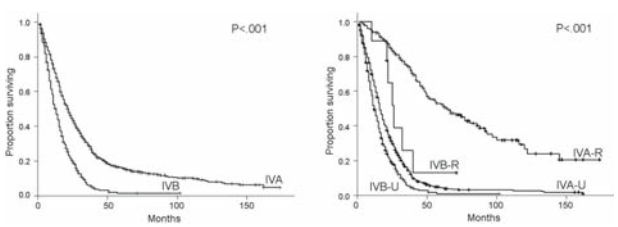
Introduction: Colorectal cancer patients with metastases beyond the regional nodes are grouped as having stage IV disease, regardless of location or treatment. The aim of this study was to develop a new staging classification to identify the variability of prognosis in patients with advanced colorectal cancer. Methods: Electronic medical records of stage IV colorectal cancer patients presenting for medical oncology evaluation at a single institution between March 1990 and September 2007 were retrospectively reviewed. Patients were classified as having liver only, extrahepatic only, or both liver and extrahepatic disease. Results: Among 1284 patients with stage IV colorectal cancer, patients presented with liver only (n=706), extrahepatic only (n=192), and both liver and extrahepatic disease (n=386). Patients with liver or extrahepatic only disease had a median overall survival (OS) of 22 months, compared to 13 months for patients with both liver and extrahepatic metastases (P<.001). Thus, patients with liver or extrahepatic only disease were staged IVA, while those with both liver and extrahepatic disease were staged IVB (Figure). Surgery with curative intent was performed in 235 patients, including 199 with liver only, 27 extrahepatic, and 9 with liver and extrahepatic disease. Five-year OS rates for resectable IVA and IVB patients were 52% and 13%, respectively, compared to 0% for unresectable IVA and IVB patients (P<.001). Thus, patients with resectable and unresectable disease were assigned modifiers "R" and "U," respectively (Figure). Among IVA-R patients, 5-year OS was 54% in patients with liver only disease and 41% in patients with extrahepatic only disease, but this difference was not statistically significant (P=.11). Treatment with modern chemotherapy, irinotecan and/or oxaliplatin, was associated with an increase in median survival from 13 to 19 months in unresectable patients (P<.001) but did not affect OS in resectable patients. Conclusion: The outcome of patients with stage IV colorectal cancer can be stratified based on extent of disease and treatment. Further validation of this proposed staging will help future studies evaluating the outcome of patients with advanced colorectal cancer.



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Cost-effectiveness of Prolonged Thromboprophylaxis After Cancer Surgery C. Bradley,* K. Brasel, J. Miller, S. Pappas. *Dept. of Surgery, Medical College of Wisconsin, Milwaukee, WI.*

Background: Consensus guidelines recommend prolonged thromboprophylaxis for up to four weeks in patients undergoing major abdomino-pelvic cancer surgery. These guidelines are rarely followed. Factors that reduce adherence to guidelines include concerns over cost, increased bleeding complications, and poor patient compliance. We hypothesized that chemical prophylaxis after discharge would be cost-effective compared to no prophylaxis. **Methods**: A cost-effectiveness model was constructed comparing 4 alternative strategies to post-discharge thromboprophylaxis in surgical oncology patients: (1) low molecular weight heparin (LMWH) once daily (2) low dose unfractionated heparin (LDUH) three times daily (3) oral aspirin (ASA) once daily (4) no prolonged prophylaxis. Probabilities and costs were estimated based on published literature and average Medicare reimbursement. The decision analysis was conducted from the perspective of the healthcare system, with the primary endpoint being cost per patient without venous thromboembolism (VTE) after 4 weeks. Sensitivity analyses tested the robustness of the results. **Results**: LDUH was most cost-effective, saving $361 per patient without VTE compared to no prophylaxis. All costs in the no prophylaxis branch are attributable to a higher VTE rate ($4717 each). LMWH was not cost-effective, incurring $190 per patient without VTE compared to no prophylaxis. When poor compliance was considered, LDUH remained the dominant strategy. However, ASA became a viable alternative when compliance with LDUH was as low as 50%, costing an additional $15 for the same benefit. A maximum bleeding rate with LDUH of 13% had no effect on the results. Sensitivity analyses failed to show any instance where LMWH was cost-effective. Based on an estimated 300,000 abdominal cancer operations yearly, LDUH would save $86M per year over no prophylaxis. **Conclusion**: While all chemical prophylaxis is effective preventing VTE in the outpatient setting after cancer surgery, LDUH is the most cost-effective, even when compliance is low. This strategy saves money overall compared to no prophylaxis and further supports recommendations for prolonged thromboprophylaxis after cancer surgery.

Cost-effectiveness of Prolonged Thromboprophylaxis in Order of Dominance.

	Cost per patient w/o VTE ($)	Absolute reduction in VTE relative to no prophylaxis (%)	Cost per patient w/o VTE relative to no prophylaxis ($)	Annual population cost relative to no prophylaxis ($)
LDUH	346	8	-361*	-86M
ASA	583	2	-124	-29M
No prophylaxis	707	0	0	0
LMWH	897	8	+190	+71M

*Negative sign = dollars saved; positive sign = dollars spent.

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Colorectal Cancer Screening Among First-degree Relatives of Colorectal Cancer (CRC) Patients: Benefits and Barriers L.A. Mack,[1]* L.S. Cook,[2] W.J. Temple,[1] L.E. Carlson,[3] R.J. Hilsden,[3] E. Oddone Paulocci.[3] *1. Surgery and Oncology, Tom Baker Cancer Center/ University of Calgary, Calgary, AB, Canada; 2. University of New Mexico, New Mexico, NM; 3. University of Calgary, Calgary, AB, Canada.*

Introduction: Individuals with a first-degree family history of CRC are at an increased risk of CRC and may be an important population for a standardized screening program. Main study objectives were: 1) To estimate the proportion of first-degree relatives (FDR) of CRC patients being screened for CRC. 2) To identify predictors of screening behavior. Methods: A questionnaire was mailed to 640 Stage I-III CRC patients from a population-based registry to identify FDR. 747 FDR, aged 40 or older, were sent a survey to assess CRC screening practices, knowledge, demographics, health care access, as well as potential benefits and barriers to CRC screening. A factor analysis of Likert scale items was used to detect constructs correlating with responses. Predictors of screening behavior were explored through a multivariate analysis (MVA) using demographic variables and results from the factor analysis. Results: There was a 54%(343/640) and 51%(383/747) response for patients and FDR respectively. Among FDR, 86% were born in Canada, 94% spoke English, 93.5% had a high school education, 73% were married and 55% had full-time employment. The age distribution was: 40-44 years (19.7%); 45-49(19.1%); 50-54(16%); 55-59(15.2%); 60-64(9.8%);>65(18%). Health care access was excellent: 93.5% had a family physician and 76% had a routine annual examination. The majority (92%) had heard of 'screening' with 79.8% noting a physician as their knowledge source. 70% had undergone CRC screening with 60% adherent to current guidelines. Overall, 33.7% had fecal occult blood testing, 19.4% had barium enema, 10.7% had sigmoidoscopy and 58.7% had colonoscopy. Factor analysis supports 5 constructs influencing CRC screening: salience and coherence, cancer worries, social influence, susceptibility, and response efficacy. MVA determined age >50 years as the most important predictor of CRC screening. Conclusion: In this survey, 70% of FDR of CRC patients had been screened for CRC; age was the most important predictor of screened status. Understanding the underlying constructs influencing screening behavior may further improve uptake of CRC screening in this population.

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Are Patients of Low Socioeconomic Status Being Denied Optimal Management for Pancreatic Cancer? M.C. Cheung,* R. Yang, L.G. Koniaris. *University of Miami Miller School of Medicine, Miami, FL.*

Objective: To define the effects of socioeconomic status (SES) and other demographic variables on outcomes for pancreatic cancer patients. Study Design: Florida cancer registry and inpatient hospital data were queried for pancreatic cancer diagnosed between 1998 - 2002. Results: A total of 16,550 patients were identified. Low SES (LSES) patients were younger at diagnosis ($p<0.001$) but presented with similar disease stage and tumor grade when compared to high SES patients. LSES patients were less likely to receive surgical extirpation (19.8% vs. 16.5%, $p<0.001$), chemotherapy (36.4% vs. 30.7%, $p<0.001$), or radiotherapy (16.9% vs. 14.3%, $p = 0.003$). Among surgical patients, 30-day mortality was significantly higher (3.5% vs. 7.3%, $p<0.001$) and 5-year survival was significantly worse in the LSES cohort (21.2% vs. 12.5%, $p<0.001$). Overall, surgical patients treated at teaching facilities (TF) did significantly better; nonetheless, increased 30-day surgical mortality (1.2% vs. 2.7%, $p<0.001$) and decreased 5-year survival (30.9% vs. 15.6%, $p<0.001$) was also observed in patients of LSES. By multivariate analysis, which corrected for patient co-morbidities, significant independent predictors of worse prognosis include LSES (HR 1.27), treatment at a non-TF (HR 1.29), and lack of surgical extirpation (HR 1.59) or chemotherapy (HR 1.69). No difference in prognosis was observed by race or ethnicity. Conclusion: Surgical extirpation and chemotherapy prolong survival for patients with pancreatic cancer. Patients of LSES are less likely to receive these therapies, have higher perioperative mortality, and worse overall survival. Greater understanding of the barriers to receiving care and causes of poor survival are needed.

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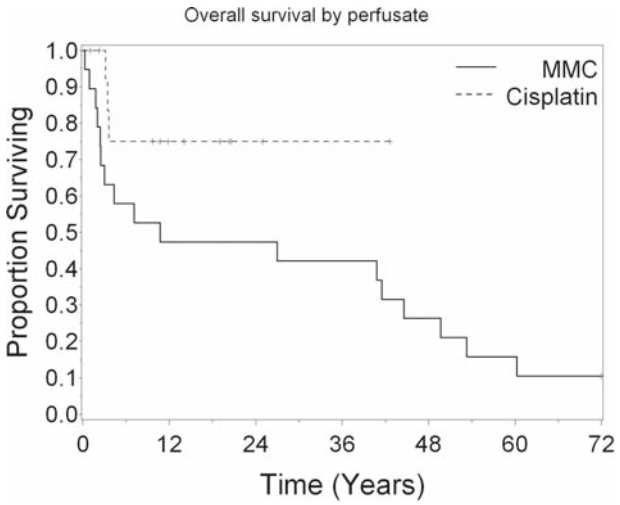
Cytoreductive Surgery with Intraperitoneal Hyperthermic Chemotherapy (IPHC) for Malignant Peritoneal Mesothelioma (MPM) A. Blackham,* G. Russell, P. Shen, J.H. Stewart, E.A. Levine. *Surgical Oncology, Wake Forest University, Winston-Salem, NC.*

Background: MPM is a rare, progressive, fatal disease with a median survival of <12 months. Systemic chemotherapy, radiation or palliative surgery have offered little survival benefit. However, cytoreductive surgery with perioperative intraperitoneal chemotherapy has been shown to significantly improve survival. The best agent to use in the peritoneal perfusate has not been established. In this prospective study, patients with MPM who underwent cytoreductive surgery combined with IPHC using mitomycin (MMC) or cisplatin in the perfusate were compared. Methods: Between August 1993 and August 2008, 34 patients with epithelioid MPM were treated with cytoreductive surgery and IPHC. IPHC with MMC was used for 19, while 15 received cisplatin. Postoperative morbidity and outcomes were compared between the two groups. Results: There were no significant differences observed in age, race, performance or resection status between the groups. Median follow-up for all patients is 3.6 years,6 years for MMC vs.1.2 for the cisplatin group. Overall survival in both groups was 52% at 3 years and 20% at 5 years with a median survival of 3.4 years. Comparing survival for MMC vs. cisplatin revealed a trend toward increased survival with cisplatin (10.8 months vs. 3.6 years, $p=0.08$), however DFI was not significantly different. Hematological toxicity was observed more often in the MMC group (Leukopenia 40% vs. 6 %,$p=.013$, and thrombocytopenia 48% vs. 17%, $p=.052$). Renal Toxicity was significantly more common in patients treated with cisplatin (61% vs. 0%, $p< .01$)). Hemodialysis was required for 3 cases

after being treated with cisplatin despite receiving sodium thiosulfate for renal protection. All patients recovered normal renal function prior to discharge from the hospital. Conclusions: Hematological toxicity is more common using MMC, while renal toxicity is more common with cisplatin. Despite the increased renal toxicity associated with cisplatin, the overall survival is better for patients receiving IPHC with cisplatin than MMC. Therefore, we recommend using cisplatin during IPHC for treatment of malignant peritoneal mesothelioma.



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Partial Nephrectomy for Selected Renal Cortical Tumors Greater Than 7 Centimeters M.E. Karellas,* P. Russo. *Surgery/Urology, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction Partial nephrectomy (PN) is the accepted surgical approach for appropriate renal cortical tumors (RCTs) less than 7cm. Recent data revealing the link between chronic kidney disease and increased mortality rates have renewed the emphasis on PN to minimize the impact of nephrectomy on long-term health. Objective To examine our institutional experience in patients treated with partial nephrectomy for RCTs 7cm or larger. Methods After institutional review board approval, we examined our surgical database for patients treated with PN for RCT 7cm or greater between July 1990 and Jun 2008. Pertinent demographic, clinical, surgical pathologic data were reviewed. Results A total of 37 patients were identified for analysis with median age of 63 years (IQR=52, 71), median tumor size was 7.5cm (7.2, 7.9) with the largest tumor being 19cm. Thirty two surgeries were open PN with 5 laparoscopic PN. Indication for PN was elective in 32 patients while 5 patients required PN for a solitary kidney from a prior radical nephrectomy. Three patients had known metastatic disease at the time of PN. Median estimated blood loss was 500mL (200, 750), median operative time 170 minutes (150, 240), median hospitalization was 4 days (3, 5). Thirty-one patients (84%) had carcinoma evident on final pathology, with 16 patients (43%) having conventional clear cell carcinoma, followed by 8 patients (22%) with papillary neoplasms. Non-cancerous pathology included multilocular cystic nephroma (3), angiomyolipoma (2), and oncocytoma (1). Median follow-up was 17 months (6, 40). Twenty-nine patients (78%) are currently alive without evidence of disease, 3 patients are currently alive with metastatic disease (2 had known pre-op metastatic disease), and 3 patients died of disease. Median creatinine change from pre-op level was 0.1 mg/dl (0, 0.3) with only 1 patient (with pre-existing chronic renal insufficiency) requiring hemodialysis postoperatively. Conclusions Our findings suggest that partial nephrectomy can effectively be performed for selected renal tumors of greater than 7cm in order to provide excellent local tumor control and maximally preserve overall renal function.