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P1

Evaluation of Phosphatidyl inositol 3-kinase catalytic subunit (PI3KCA) and Epidermal Growth Factor Receptor (EGFR) gene mutations in pancreatic adenocarcinoma R. Iyer,[1]* M. Rossi,[2] M. Javle,[3] K. Lo,[1] J. Cowell,[1] N. Khushalani,[1] B. Kuvshinoff,[1] J. Gibbs.[1] *1. Roswell Park cancer Institute, Buffalo, NY; 2. Yale University, Hartford, CT; 3. MD Anderson Cancer Center, Houston, TX.*

Introduction: Phosphatidyl inositol 3-kinase (PI3K) activation involves EGFR and platelet derived growth factor receptor and has been shown to play an important role in cell survival signaling in a number of cell types including pancreatic cancer. Presence of specific mutations in the EGFR gene have been shown to correlated with clinical response to the tyrosine kinase inhibitor gefitinib in patients with advanced non small cell lung cancer. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Mutations in PIK3CA, a member of the family of phosphatidylinositol 3'-kinase catalytic subunits have been shown to correlate with a poor outcome in brain tumors. The aim of this study was to examine the prevalence of PI3KCA and EGFR mutations known to have prognostic value in other tumor types in this population where EGFR inhibition has become standard of care. Methods: With approval from the IRB, 30 cases of pancreatic carcinoma that underwent Whipple procedure at Roswell Park Cancer Institute between 12/1/1999 and 11/30/2004 were identified. Using exon specific primers, genomic DNA was extracted from formalin fixed paraffin embedded tumor and adjacent normal tissue. This was used to PCR amplify exons 9 and 20 of the PIK3CA gene and exons 18-21 of the EGFR gene. The PCR products were gel purified and sequenced using an Applied Biosystems' PRISM 3100 Genetic Analyzer (Foster City, CA). Results: One synonymous SNP (rs1050171) was identified in the coding region of EGFR. A previously unreported change, suspected to be a SNP, was observed in intron18 of EGFR (IVS18+15, C>T). No mutations in either PIK3CA or EGFR genes were identified for any of the tumor samples that were analyzed. Conclusions: In this small study, we did not observe any of the "hot spot" mutations in either EGFR or PIK3CA in the 30 tumor samples that were analyzed. Screening for EGFR or PIK3CA mutations in pancreatic cancer may not be helpful in determining prognosis or response to EGFR inhibition.

P2

Comparative Genetic Expression Profile of Gemcitabine (GEM) Sensitivity in Pancreatic Cancer (PC) Cells A. Razzak,* A. Saied, J. Hering, J. Trevino, N. Espat. *Surgical Oncology, Roger Williams Hospital, Providence, RI.*

The genetic profile following GEM treatment of the PC cell line L3.6pl (GEM-sensitive) was compared to a GEM-resistant clone (L3.6 clone). METHODS: L3.6pl cells were cultured by standard protocol. GEM resistance was induced by exposure to 500 ng/ml of GEM, 5x greater than the IC50, for 48 hours, and increased to 3000 ng/ml in 500 ng/ml increments. GEM resistance was confirmed by sustainment in DMEM (without GEM) for 6-wks with no effect on proliferation when returned to maintenance GEM (125ng/ml). Cells were treated with 100µM GEM or media-only for 12 hours, RNA was extracted using Qiagen RNeasy columns; quality confirmed spectrophotometricaly, gel electrophoresis and an Agilent 2100 bioanalyzer. Microarray analysis performed using Agilent 44K whole human genome 60mer oligonucleotide array, containing 41,000 unique gene sequences. Data analysis performed using Agilent software and normalized using LOESS regression on all background corrected signal intensities. Significant differential expression (SDE) defined as ≥ 2 fold difference between GEM and media-only controls. A fold-change value of 1 was assigned to all spots ≤ the median value background intensity. RESULTS: 3352 SDE genes in L3.6pl vs. 3274 genes in L3.6 clone relative to control were identified. By gene ontology, 225 SDE genes that regulate transcription, 32 regulating apoptosis, 29 regulating cell proliferation, 21 regulating cell cycle, 20 involved with inflammation and 13 regulating cell cycle arrest in L3.6pl. L3.6 clone data revealed 118 SDE genes regulating transcription, 9 regulating apoptosis, 19 regulating cell proliferation, 16 regulating cell cycle, 10 involved with inflammation and 8 regulating cell cycle arrest were observed. (Table 1. is representative) CONCLUSION: Using a PC cell line intrinsically sensitive to GEM and comparing it to a GEM resistant clone revealed a differential genetic expression profile. These data support investigation for the potential chemosensitization of PC, planned studies include: microarray result confirmation by RT-PCR and 2) experiments to target identified altered genes as a means to augment chemosensitivity of PC to treatment.

Table 1. Select Genetic Expression Profile of Gemcitabine Sensitivity L3.6pl vs. L3.6 Clone

Gene Symbol	Gene Description	Fold Change* L3.6pl	Fold Change* L3.6 Clone
Highly Differentially Expressed Genes			
BQ130701	Human insulinoma Homo sapiens cDNA clone similar to SW:CTGF_HUMAN P29279 CONNECTIVE TISSUE GROWTH FACTOR PRECURSOR, mRNA Sequence	2.60	7.53
ALOX15B	arachidonate 15-lipoxygenase, type B, transcript variant d	2.32	7.08
TNK1	tyrosine kinase, non-receptor, 1	2.60	6.30
CEACAM1 (BGP1)	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein), transcript variant 2	1.03	-8.16
EFCBP2	EF hand calcium binding protein 2	1.00	-11.01
OPHN1	oligophrenin 1	1.00	-12.81
Gemcitabine Metabolism Genes			
DCK	deoxycytidine kinase	1.08	1.68
RRM1	ribonucleotide reductase M1 polypeptide	1.14	1.74
RRM2	ribonucleotide reductase M2 polypeptide	1.23	1.33
h-ENT1 (SLC29A1)	solute carrier family 29 (nucleoside transporters), member 1	-1.11	-1.24
Apoptosis Genes			
CASP7	caspase 7, apoptosis-related cysteine peptidase, transcript variant gamma	1.10	2.10
BIRC3	baculoviral IAP repeat-containing 3, transcript variant 1	4.20	1.61
BCL2	B-cell CLL/lymphoma 2, nuclear gene encoding mitochondrial protein, transcript variant alpha	-1.30	2.14
Cell Cycle Mediator Genes			
TP53	tumor protein p53 (Li-Fraumeni syndrome)	3.02	-1.84
CDKN1A ($p21^{waf}$/$p21^{cip}$)	cyclin-dependent kinase inhibitor 1A, transcript variant 1	1.90	1.02
GADD45A	growth arrest and DNA-damage-inducible, alpha	6.21	-1.27
CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	4.04	1.22
CDKN2B	cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4), transcript variant 2	2.32	-1.00
Inflammatory Genes			
NFKB1 (p105)	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	2.23	1.08
NFKB2 (p49/p100)	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2	2.04	-1.38
NFKBIE	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	3.62	1.52
IL1A	interleukin 1, alpha (IL1A), mRNA	3.92	-1.00
IL6	interleukin 6 (interferon, beta 2)	2.70	-1.00
TNF	tumor necrosis factor (TNF superfamily, member 2)	3.62	2.18

*Fold change is calculated relative to media-only (DMEM) control treatment. Significance is defined as ≥ 2-fold change in expression of normalized background subtracted signal intensities. Genetic Expression of genes with signal intensity ≤ median value background intensity were assigned fold change value = 1. Negative numbers denote down-regulation relative to control (DMEM).

P3

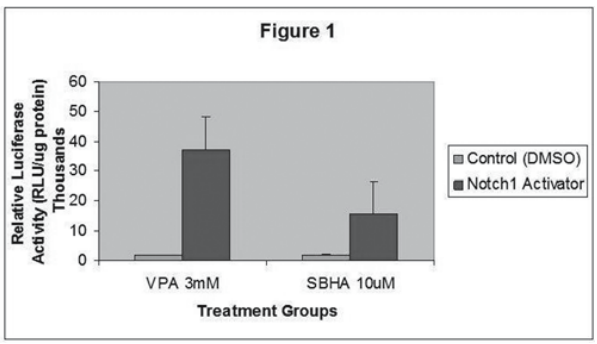
5-Fluorouracil Resistance in Colorectal Cancer Cells Leads to Epithelial-Mesenchymal Transition and Enriches for Tumor Stem Cells N.A. Dallas,* L. Xia, F. Fan, A.D. Yang, S.J. Lim, M.J. Gray, S. Samuel, P. Gaur, L.M. Ellis. *Department of Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX.*

Introduction: 5-fluorouracil (5FU) is the foundation for therapy in patients with metastatic colorectal cancer (CRC). Resistance to 5FU occurs in nearly all patients with metastatic CRC. This study determined the phenotypic and molecular alterations associated with 5FU resistance. Methods: The human CRC cell line HT29 was exposed to increasing doses of 5FU to achieve resistance at 2 µg/ml (clinically relevant dose), (HT29/5FUR). Cell count was determined by MTT assay. Migration was assessed in Boyden chambers. Anchorage-independent growth was determined in soft agar assays. Western blotting and flow cytometry were done to determine molecular alterations including epithelial-mesenchymal transition (EMT) and tumor stem cell markers. Results: HT29/5FUR cells exhibited a spindle-shaped morphology with increased migration and invasion. The epithelial markers E-cadherin, plakoglobin, and ZO-1 were decreased in HT29/5FUR cells, consistent with EMT similar to prior studies in oxaliplatin (Ox)-resistant cells (HT29/OxR). HT29/5FUR cells exhibited increased anchorage independent growth. HT29/5FUR and HT29/OxR demonstrated 16- to 30-fold enrichment of CD133+ cells and 2-fold enrichment of CD44+ cells, CRC stem cell markers. Resistant cells were enriched 5- to 30-fold for double-positive (CD133+/CD44+) cells. Consistent with the tumor stem cell phenotype, HT29/5FUR cells exhibited a decrease in cellular proliferation (46%). Levels of phosphorylated IGF-1-receptor (IGF-1R) were increased in both resistant cell lines. HT29/5FUR and HT29/OxR cells were ~5-fold more responsive to IGF-1R inhibition relative to parental cells ($p<0.01$). Conclusion: 5FU resistance causes morphologic and signaling changes in CRC cells that lead to distinct alterations consistent with EMT. 5FU and Ox resistance enriches cells for those that express tumor stem cell markers and were more sensitive to IGF-1R inhibition. Identification of molecular targets of chemo-resistant CRC cells will allow for the rational development of targeted therapies for patients with metastatic CRC.

P4

A novel reporter gene assay for high throughput screening of Notch1 activators in a human carcinoid cancer cell line S.N. Pinchot,* R. Jaskula-Sztul, M. Kunnimalaiyaan, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

Background: Besides surgery, there are limited curative and palliative treatments available to patients with gastrointestinal (GI) carcinoids. Activation of the Notch1 pathway has been shown to reduce both NE markers including chromogranin A (CgA) and serotonin, and cellular proliferation in GI carcinoid cells. Identification of compounds capable of pharmacologically activating Notch1 expression therefore represents a potential therapy for patients with GI carcinoids. Methods: To create a NE cell line capable of detecting molecules which activate Notch1 signaling, BON human GI carcinoid cells were stably transfected with a centromere-binding factor 1 (CBF-1) -luciferase reporter vector. Notch1 binding to CBF-1, an ubiquitous transcription factor, is required for downstream activation of the Notch1 pathway. After selection, the resulting BON-CBF1-LUC cell clones were treated with valproic acid (VPA) or suberoyl bis-hydroxamic acid (SBHA), compounds recently shown to activate Notch1 signaling in carcinoid cells, as well as control DMSO. Luciferase assays were performed on cellular lysates after 48 hours of drug exposure. Results: Treatment of BON-CBF1-LUC cells with Notch1 activating compounds resulting in high induction of luciferase in several clones. Importantly, there was minimal luciferase detected in the DMSO-treated cells. Of the stably transfected clones, the 23M11 clone exhibited a 22-fold increase and an 8-fold increase in luciferase activity following treatment with VPA and SBHA, respectively, relative to control (figure 1). Conclusion: The BON-CBF-1-LUC cell system provides a novel and sensitive reporter gene assay for high throughput screening of selective activators of the Notch1 pathway. Furthermore, identification of Notch1 activators holds potential for expanding the therapeutic and palliative treatment of patients with carcinoid tumors.



P5

Inhibition of Smad 3 Action is Mediated by Cyclin E Overexpression in Breast Cancer Cells S. Ghosh, K.S. Bryce, J.S. Jeruss.* *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: Activin, a growth factor in the TGF-β superfamily, triggers the activation of Smad 3, a transcription factor that contributes to G1 cell cycle arrest in breast cancer cells. Overexpression of cyclin E, another key cell cycle regulatory protein, and its low molecular weight (LMW) forms, have been associated with poor prognosis in breast cancer. Cyclin E has been shown to mediate phosphorylation of the Smad 3 linker region by cyclin dependent kinases (CDK), resulting in inhibition of Smad 3 activity. We hypothesize that overexpression of cyclin E may exert tumorigenic effects through the functional inhibition of Smad 3 in breast cancer cells. Methods: Western blotting was implemented to evaluate the basal protein expression of Smad 3 and phosphorylated activated Smad 3 (phospho-Smad 3), in vector control MCF-7 cells and a LMW cyclin E overexpressing MCF-7 breast cancer cell line. To determine the impact of cyclin E overexpression on Smad 3 function, wild-type (WT) or linker region CDK phosphorylation site mutated Smad 3 constructs were co-transfected with a Smad 3 reporter into the vector control MCF-7 and the LMW cyclin E overexpressing MCF-7 cells. Smad 3 function was then evaluated by luciferase reporter assay. Results: MCF-7 cells overexpressing the LMW cyclin E expressed a higher level of phospho-Smad 3 as compared to the vector control cells, while total Smad 3 levels remained unchanged. Expression of the linker region mutated Smad 3 in control cells resulted in greater than three-fold induction in Smad 3 reporter activity compared to the WT Smad 3. Interestingly, expression of the linker region mutated Smad 3 in MCF-7 cells overexpressing the LMW cyclin E, resulted in an eight-fold induction of the Smad 3 reporter, as compared to the WT Smad 3. Conclusions: This study indicates that overexpression of a LMW form of cyclin E may circumvent the growth inhibitory effects of activin/Smad 3 signal transduction through the blockade of Smad 3 function. The overexpression of phospho-Smad 3, found in the LMW cyclin E cells, may be a compensatory mechanism by activin/Smad 3 signaling to surmount the tumorigenic effects of LMW cyclin E in these cells.

P6

In Vivo Therapy with GM-CSF Markedly Expands the Number of Kupffer Cells and Enhances their Innate and Adaptive Immune Function S.C. Katz,* T.P. Kingham, U.I. Chaudhry, J.R. Raab, R.P. DeMatteo. *Surgery, Memorial Sloan-Kettering, New York, NY.*

Introduction: Kupffer cells (KC) are an integral component of the hepatic response to infection and malignancy. We tested the ability to expand KC in vivo using the cytokine GM-CSF, a growth factor for monocytic cells. Methods: C57Bl/6 mice were given a single intravenous injection of saline, recombinant adenovirus (Ad), or adenovirus encoding GM-CSF (AdGM). One week later, KC phenotype was analyzed by flow cytometry. T cell stimulatory ability, uptake of fluorescent E. coli, and cytokine response to LPS were also tested. KC were isolated by cell surface marker expression. Potentially confounding dendritic cells, endothelial cells, and neutrophils were definitively excluded. Results: We found that the number of KC in murine livers was markedly lower than previously reported (Table).There was a greater than 100-fold increase in the number of KC one week after AdGM administration which was accompanied by marked hepatomegaly. Expansion of KC was noted as early as 3 days after AdGM injection. KC from all groups had typical macrophage features under light microscopy and expressed the macrophage markers CD11b, F4/80, and CX3CR-1. KC from each group demonstrated nitric oxide production in response to IFN-γ as further confirmation of macrophage lineage. The innate immune function of expanded KC was enhanced as evidenced by increased phagocytosis of E.coli and increased TNF-α secretion in response to LPS. KC from AdGM treated animals also demonstrated a greater capacity for acquired immunity through enhanced T cell stimulation. Both allogeneic and antigen-specific CD4 and CD8 T cell proliferation was increased in AdGM-expanded KC compared to controls despite stable levels of MHC class II and CD86 expression. Discussion: Endogenous GM-CSF overexpression leads to massive expansion of KC with enhanced immunostimulatory properties. GM-CSF therapy may have therapeutic application to primary and secondary hepatic malignancies.

Group (n=3)	#KC ($x10^5$)	CD4 Ag Specific ($CPMx10^3$)	CD8 Ag Specific ($CPMx10^3$)	TNF-α (pg/ml)
Saline	8±3	22±7	76±3	646±113
Ad	18±4	68±5	68±9	1129±82
AdGM	1008±53*	119±11*	160±19*	2440±383*

*p<0.05

P7

Dendritic Cells Pulsed with Keyhole Limpet Hemocyanin and Cryopreserved Maintain Their *In Vivo* Function upon Intratumoral Administration S. Teitz-Tennenbaum,* Q. Li, M. Davis, A.E. Chang. *Division of Surgical Oncology, University of Michigan, Ann Arbor, MI.*

Introduction: We compared the viability, phenotype, and therapeutic efficacy of murine bone marrow-derived unpulsed dendritic cells (UP-DC), DC pulsed with keyhole limpet hemocyanin (KLH-DC), and cryopreserved KLH-DC (C-KLH-DC) upon intratumoral (i.t.) vaccination combined with radiotherapy. Methods: Viability was evaluated using trypan blue exclusion and 7-AAD staining. Expression of MHC I, MHC II, CD80, CD86, CD40, and CD11c was examined using fluorochrome-conjugated monoclonal antibodies and flow cytometry. DCs pulsed with LPS served as a positive control for induction of

maturation. To assess *in vivo* function, C57BL/6 mice were inoculated s.c. with D5 melanoma cells on day 0. DC were injected i.t. on days 6, 11, 14, and 18. Local tumor irradiation was delivered in 5 consecutive daily fractions of 8.5 Gy. Tumors were measured 3 times a week, and data were compared by analysis of variance. Results: Mean percentage ± SE of viability of UP-DC, KLH-DC, and C-KLH-DC by trypan blue exclusion was 93.1 ± 1.3, 95.1 ± 0.8, and 87.3 ± 2.3, respectively. Analysis of 7-AAD stained cells confirmed these results. While pulsing DC with LPS up-regulated all cell surface markers, KLH pulsing increased only expression of MHC II. Immediately after thawing, C-KLH-DC expressed slightly decreased levels of MHC I, CD80, CD86, and CD11c. I.t. administration of UP-DC, KLH-DC, or C-KLH-DC alone inhibited tumor growth to the same extent ($p \leq 0.001$ versus i.t. PBS). Radiotherapy alone inhibited tumor growth as well ($p < 0.001$ versus PBS). Combined therapy with radiation plus UP-DC, KLH-DC or C-KLH-DC further inhibited tumor growth compared with all monotherapies ($p < 0.02$ versus all other groups except combined therapy), but to the same extent. Conclusions: Cryopreservation of KLH-DC slightly reduces viability and expression of co-stimulatory cell surface markers, however *in vivo* anti-tumor activity is fully maintained with or without radiotherapy. Adding KLH to DC-based tumor vaccines facilitates monitoring of induced immune responses. Since DC generation is labor-intensive, use of cryopreserved aliquots will be helpful for clinical application.

P8

Improved Testing for Microsatellite Instability in Colorectal Cancer
I.O. Esemuede,[1]* A. Forslund,[1] M. Gimbel,[1] G. Nash,[1] Z. Zeng,[1] S. Rosenberg,[1] M. Weiser,[1] F. Barany,[2] P. Paty.[1] *1. Memorial Sloan-Kettering Cancer Center, New York, NY; 2. Weill Medical College of Cornell University, New York, NY.*

In colorectal cancer, microsatellite instability (MSI+) is a valuable marker of defective DNA mismatch repair that identifies cancers with distinct phenotypic properties, including favorable survival. However, there is no concensus regarding the optimal assay for MSI status . We have evaluated a simplified three marker assay for MSI and compared it to the traditional five marker NCI consensus panel assay to see if technical variations in MSI testing are important. Methods: DNA samples from 357 snap frozen primary CRCs were evaluated. Microsatellites for the three marker assay (at least 2 of 3 positive: BAT25, BAT26, D2S123) and the NCI five marker assay (at least 2 of 5 positive: BAT 25, BAT26, D2S123, D5S346, D17S250) were objectively tested for size instability using fluorescently labeled PCR primers, an ABI DNA analyzer, and Genotyper software. Braf V600E mutations were detected by a validated PCR/LDR assay. For 28 cases, genome wide copy number aberrations were evaluated using Agilent 244K arrays. Clinical data was obtained from a prospective database and confirmed by chart review. Median follow-up was 60 months. Data: The NCI 5-marker assay identified 96 cancers as MSI+. Only 56 of these were MSI+ by the 3-marker assay, leaving 40 cases identified as MSI+ only by NCI criteria. The remaining 261 cancers were microsatellite stable (MSS) by both assays. Clinical and genetic features of the identified groups were assessed as shown in figure below. On Agilent chip analysis, gain or loss of at least one chromosomal arm was observed in 2 of 16 MSI+ cancers (3-marker assay), 3 of 4 NCI MSI+ cases, and 7 of 8 MSS cases ($P < 0.001$). Conclusion: The 3-marker MSI assay significantly outperforms the traditional 5-marker MSI assay for identifying patients with favorable prognosis and homogenous clinical and genetic features. More accurate MSI testing should improve prognostic and predictive scoring systems for colon cancer.

MSI Data

	NCI 5-marker MSI+ (N = 96)		MSS (N=261)
	3-marker+ cases (N=56)	remaining NCI cases (N=40)	
HNPCC (Amsterdam 2)	14%*	0%	0.4%
Right sided CRC	68%*	38%	30%
High grade histology	25%*	8%	8%
BRAF mutations	34%*	3%	3%
Stage IV	7%#	28%	28%
5-yr survival	88%*	67%	62%

* $P < 0.02$, # $P < 0.05$ for comparisons to NCI+ cases and MSS cases

P9

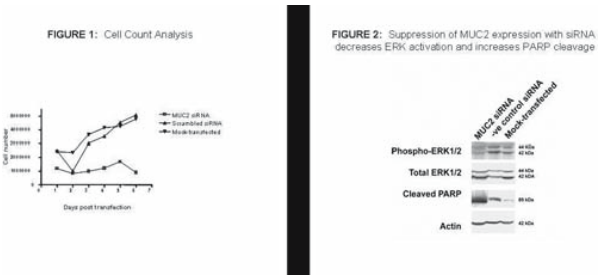
Stat1 Pathway may Mediate Tumor Virulence and/or Metastagenicity
P.B. Roach,* T. Darga, H. Mauceri, M. Bhayani, M.C. Posner, R.R. Weichselbaum, N. Khodarev. *Surgery, University of Chicago, Chicago, IL.*

Introduction: Using tumor selection by irradiation and serial passage we identified a genetic signature associated with resistance to DNA damage and interferon (IFN). This signature represents a Stat1 pathway associated with IFN signaling. We tested whether this pathway is associated with tumor virulence and /or metastagenicty. Methods: B16F1 cells were passed using i.v. injection ("P1 passage") through wild-type C57Bl6 mice. Tumor clones metastasizing to lungs were harvested, grown in vitro into distinct cell lines, and individually profiled for the Stat1 pathway by QRT-PCR. Cell lines upregulating the Stat1 pathway after P1 passage [P1(+)], and those downregulating it [P1(-)], were then separately passed i.v. through a second generation of mice ("P2 passage") and profiled by QRT-PCR. Progeny of P1(+) cells were called P2(+), and that of P1(-) called P2(-). P2(+) cell lines were passed in animals again, and corresponding cell lines (P3) were profiled in similar fashion as P1 and P2. Results: P1 passage of B16F1 cells through twenty mice resulted in nineteen distinct cell lines, eight of which were from pulmonary metastases: Three P1(+), five P1(-). In P2 passage the overall efficiency of P1(-) cell line colonization was low and comparable to that of B16F1, whereas P1(+) clones colonized animals with ten-fold higher efficiency. P2(+) cell lines were more resistant to IFN gamma and IR than P2(-). QRT-PCR analysis revealed expression of the Stat1 pathway in P2(+) cell lines to be significantly higher (x2-10 fold) than in P2(-) cell lines. Accordingly, expression of Stat1 pathway was higher in P3 cell lines compared to P2 cell lines. Subcutaneous tumor growth was noted to be 2x greater in P3 cell lines versus P2(+) tumors and F1 tumors. Conclusion: Tumors that over-express the Stat 1 pathway demonstrate more virulent growth and ability to metastasize to the lungs than tumor cells that do not over-express this pathway. Stat1 over-expression and tumor virulence/metastagenicity correlates with resistance to IFN gamma and IR. Our data suggest that such combined resistance is associated with suppression of apoptotic response and develops as the result of tumor/host interactions.

P10

Novel illustration that MUC-2 overexpression promotes tumor growth by autocrine cellular events and signaling
J.M. Foster,* T. El-Abaseri, B.W. Loggie. *Surgery, Creighton University, Omaha, NE.*

Introduction: Mucinous colorectal cancers have been identified as a highly aggressive phenotype presenting with more advanced disease and a poor prognosis. The biological mechanisms involved are unclear, but appear to be linked to mucin glycoprotein overexpression like MUC-2. Many groups including ours has shown that abrogation of MUC-2 expression in the highly tumorogenic LS174T colorectal cancer cell line results in decreased 'in vivo' tumor growth and metastasis in mouse models. However, the biological events and molecular pathways modulated by MUC-2 our still unknown. In this project we report the first evidence of autocrine cellular regulation, as well as, perk & PARP expression by modulating MUC-2 expression in LS174T cells. Methods: LS174T colon cancer cells were grown 'in vitro' and MUC-2 expression was inhibited by MUC-2 small interfering RNA molecules(siRNA). Cell counts were measured to determine the overall effect on viability. Proliferative effects were measured by MUH assay and S-phase fraction; with concomitant western analysis for perk expression. Apoptotic events were measured by TUNEL immunostaining assay, while molecular confirmation of apoptosis was monitored by PARP cleavage western blot. Results: Upon treatment with MUC-2 siRNA there was a significant reduction in cell counts on days 1-6(Fig 1). A significant reduction in proliferation was found with MUC-2 inhibition, evident by a 40% reduction in MUH proliferation assay and a 2-fold increase in S-phase arrest. Concurrently, there was significant reduction in perk expression(Fig 2). A significant increase in apoptotic activity was demonstrated by increased TUNEL staining and PARP expression(Fig 2). Conclusion: MUC-2 expression appears essential for maintenance of LS174T cell viability. Biologically, MUC-2 expression promotes proliferation mediated through MAPK/erk signaling and inhibits apoptosis in LS174T colon cancer cells. These novel results, our the first demonstration that MUC-2 expression has autocrine regulatory effects in colorectal cancers that needs further investigation, and supporting efforts to develop therapies that target MUC-2.



P11

shRNA Silencing of the RON Receptor Tyrosine Kinase Results in Apoptosis and Necrosis of Pancreatic Cancer Xenografts

J.M. Logan-Collins,[1]* W. Stuart,[1] S. Waltz,[1] A.M. Lowy.[2] *1. University of Cincinnati Medical Center, Cincinnati, OH; 2. Univeristy of California San Diego Medical Center, San Diego, CA.*

INTRODUCTION The RON tyrosine kinase receptor has recently been implicated in the progression of pancreatic cancer. Studies of cultured pancreatic cancer cells have linked RON to regulation of the MAPK and PI3K/AKT signaling pathways and oncogenic phenotypes such as apoptotic resistance, tubulogenesis and invasion. No studies have investigated the importance of RON signaling to pancreatic cancer cell growth in the in vivo setting. This study investigates RON-dependent signaling and phenotypic changes using a murine xenograft tumor model. METHODS XPA, a RON-expressing pancreatic cancer cell line, was stably transfected with a RON-silencing shRNA plasmid vector. The resulting cell line and corresponding controls were used to develop subcutaneous tumor xenografts in nude mice. Protein expression was evaluated by ELISA and Western blot (WB) analysis. Tumor xenografts were evaluated for latency, growth and tumor volume at the time of harvest (30 days). Additional studies included H&E, and immunohistochemistry for proliferation (BRDU), microvessel counts (CD31), and apoptosis (TUNEL) assays. Statistical analysis was performed with one-way ANOVA. RESULTS RON expression was reduced by 90% in both the stable XPA shRNA cell line and the resulting shRNA tumor xenograft. While there appeared to be no difference in tumor latency, volume or proliferation rates, there was a 74% increase in apoptotic cells (TUNEL) and an 88% increase in necrosis (H&E) in the RON-silenced group over untransfected controls (Figure 1A and B). Significant decreases in MAPK and phospho-AKT expression were observed in the RON-silenced tumor group (50% and 66% respectively, Figure 1C). Interestingly, in viable areas of the tumor, there was a 25% increase in microvessel counts by CD31 in the RON-silenced group. CONCLUSION These results establish that, in vivo, RON receptor signaling; 1) is required for maintenance of pancreatic cancer growth and 2) regulates the MAPK and PI3K/AKT pathways. Given the success of targeting receptor tyrosine kinases in cancer therapeutics, further investigation of RON and its role in pancreatic cancer is warranted.

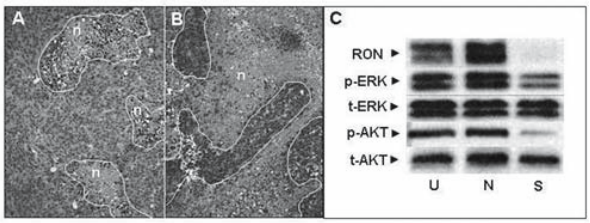


Figure. Effect of RON-silencing in vivo. H&E staining of control (A) vs RON-silencing shRNA transfected tumors (B) demonstrates a significant increase in necrosis. n = necrotic areas (C) Western blot analysis of tumor lysates reveals significant decrease in p-ERK and pAKT in RON-silenced tumors. U = untransfected, N = non-silencing shRNA transfection, S = RON-silencing shRNA transfection

P12

Use of Near-Infrared Imaging for Detection of Tumors in vivo

S.W. Baldwin,[1]* J. Smallwood,[1] J. Moretz,[2] S. Nwosu,[2] M.E. Reeves.[1] *1. Loma Linda VAMC, Loma Linda, CA; 2. Loma Linda University Medical Center, Loma Linda, CA.*

Introduction: Quantification of tumor burden in animal models is critical for the development of novel anti-neoplastic agents. Recently, there have been important advances in the detection of tumor burden in vivo; however, many of these are difficult to use, prohibitively expensive, or both. Near-infra red imaging is a novel, easy to use, and relatively inexpensive method for the detection of tumor burden in vivo. Methods: A hemi-spleen nude mouse model was used to establish liver metastasis with human colorectal cancer cells. IRDye 800CW, which has a NHS ester reactive group, was coupled to monoclonal antibody specific to human MHC class I. 50 microliters of labeled antibody was intravenously injected via a retro-orbital injection into tumor bearing nude mice. Eight hours later the mouse was anesthetized with isoflurane gas and imaged using the Odyssey Infrared Imaging System. After imaging, the mouse was euthanized to directly quantify tumor burden. Results: Direct comparison between the image obtained by the Odyssey and actual tumor burden of the mouse was done. The liver tumor burden is clearly visualized by the Odyssey after 8 hours with minimal background detected at that time. There is excellent correlation between actual tumor burden and tumor detected by imaging (Figure 1). A small area of local recurrence on the left side was not detected on imaging. This is most likely due to the fibrotic and avascular nature of the local recurrence. Conclusions: Near-Infrared imaging is an easy, relatively inexpensive method for detection of tumor in vivo. Use of this technique may allow for relatively inexpensive analysis of the kinetics of tumor growth, since animals can be repeatedly imaged over time.

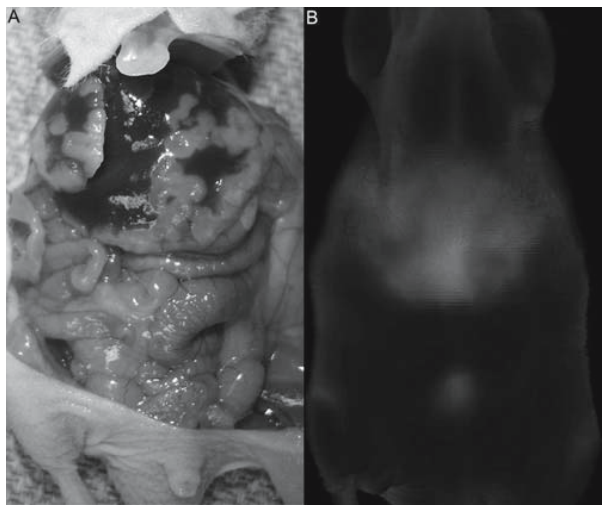


Figure 1.
A. Post-mortem of mouse showing liver infiltrated by tumor.
B. Image obtained from Odyssey showing signal in area of liver.

P13

Tgfβr1 Haploinsufficiency Reduces the Level of Phosphosmad-2 and Prevents Murine Mutant Kras-Induced Pancreatic Precancer

M. Strouch,[1]* K. Adrian,[1] M.R. Barron,[1] Y. Xu,[1] S. Phukan,[1] M. Sadim,[1] B. Pasche,[1] A. Discristofano,[2] P.J. Grippo,[1] D.J. Bentrem,[1] Q. Zeng. *1. Northwestern University, Chicago, IL; 2. Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Transforming Growth Factor Beta (TGFβ) signaling has been implicated in pancreatic tumor development. In vivo loss of either Smad4 or Tgfbr2 promotes pancreatic adenocarcinoma in mice expressing mutant Kras. Conversely, pharmacologically-reduced Tgfbr1 kinase activity attenuates growth and metastasis of PANC-1 cells when orthotopically injected into

mouse pancreas. To further evaluate the role of Tgfbr1 in pancreatic cancer development, the effects of loss of Tgfbr1 in vivo were examined. Methods: El-Kras (K) mice were crossed with Tgfbr1+/- mice (B1) to generate El-Kras/Tgbfr1+/- (KB1) and two El-Kras/Tgfbr1+/+ mice (K). Two KB1 mice and two K mice were euthanized at 6-7 months of age to compare the incidence and frequency of precancerous lesions in the pancreas. Immunohistochemistry for phosphosmad-2 was performed on pancreata of both K and KB1 mice to assess functional downstream signals following loss of Tgfbr1. Results: We observed a 50% decrease in the incidence of precancerous lesions in KB1 mice as compared to 100% in K mice. The frequency of precancer was also reduced from 11 lesions per random section of pancreas to 3, representing a 3.5-fold decrease. Furthermore, the levels of fibrosis around pre-cancerous lesions and normal-appearing parenchyma were dramatically reduced in KB1 mice. In addition, KB1 mice showed reduced lipoatrophy and lymphocytic infiltration compared to their K mice counterparts. Finally, there was a significant decrease in phosphosmad-2 expression in the pancreas and precancer lesions of KB1 mice compared to K mice, suggesting a functional effect from loss of one Tgfbr1 allele. Conclusions: Loss of either Smad4 or Tgfbr2 has led to more aggressive disease in mice with mutant Kras expression. Tgfbr1 heterozygous loss generated a significantly reduced propensity for developing carcinoma in situ and accompanying phenotypes (reduced fibrosis and inflammation). These findings were correlated with decreased expression of phosphosmad-2, suggesting that Tgfbr1 haploinsufficiency may have a protective role with respect to pancreatic cancer development and serve as a target for future therapeutics.

P14

Increased T-cell and NK cell activation after cryoablation followed by intratumoral injection of immature dendritic cells M.S. Sabel,* G. Su, A.E. Chang. *Surgical Oncology, University of Michigan, Ann Arbor, MI.*

Introduction: Although cryoablation appears to induce a cryo-immunologic response, the systemic T-cell response after cryoablation alone appears limited. To improve upon this, we examined the combination of cryoablation and intratumoral immature dendritic cells (DC) to potentate the anti-tumor T-cell response. Methods: C57Bl6 mice with B16 melanoma underwent cryoablation, intratumoral (i.t.) injection of bone-marrow derived immature DC, both, or no treatment. I.T. injection of DC occurred on day 1 and 3 after cryoablation. Tumor draining lymph nodes (TDLN) and splenocytes were assessed for specific anti-tumor response by IFNλ release assay and ELISPOT. Mice with established pulmonary metastases were sacrificed for enumeration of pulmonary metastatic nodules after treatment of the primary tumor. Results: On both IFNλ release assay and ELISPOT, lymphocytes from the TDLN and spleens demonstrated a significant and substantial increase in tumor-specific T-cell response in mice treated by cryoablation followed by i.t. DC compared with cryo alone, i.t. DC alone or untreated mice. FACS analysis demonstrates a decrease in DC number within TDLN after cryo compared with untreated mice. However, there is a dramatic increase in Cd11c+ DC number in TDLN after intratumoral injection of immature DC into cryoablated or untreated tumors. While all three treatment arms were effective compared with untreated controls, treatment of the primary tumor with cryoablation and i.t. DC led to a significant decrease in pulmonary metastases compared with either cryo alone or i.t. DC alone. This response is abrogated when mice are depleted of NK cells suggesting an increase in NK cell activity following cryoablation and i.t. DC. Discussion: Although cryoablation inhibits DC migration to the TDLN, this is reversed by the intratumoral injection of DC into the cryoablated tumor. This combination both increases the number of tumor-specific T-cells in the TDLN and splenocytes and increases NK cell activity compared with cryoablation alone or i.t. DC alone.

P15

Pathological characteristics of breast tumors in African American women treated within an equal-access health-care system: biological and molecular contributions to the aggressive phenotype and poor clinical outcomes R. Ellsworth,[1]* J.A. Hooke,[2] C.D. Shriver.[2] *1. Windber Research Institute, Windber, PA; 2. Walter Reed Army Medical Center, Washington, DC.*

Introduction: Incidence of breast cancer is higher in young African American (AAW) compared to Caucasian women (CW) and is associated with poor clinical outcome. These differences have often been attributed to access to quality-health care. >600 AAW have enrolled in the Clinical Breast Care Project (CBCP) through the equal-access health care system provided by the Department of Defense. Epidemiological and pathological factors were compared in AAW and CW with invasive breast cancer to identify environmental and biological factors associated with aggressive tumor phenotype and poor clinical outcome. Methods: Information for over 500 demographic and pathological fields was collected. Data was analyzed patients from patients with invasive breast cancer who were self-described as CW (n=356) or AAW (n=84) using Student's t-test and exact unconditional tests; a significance value of $P<0.05$ was used for all analyses. Results: Education, co-morbidity, age of menarche, age at first parity, exercise, BMI and use of screening mammogram did not differ significantly between the two groups. A significantly higher proportion of AAW performed monthly BSE, used oral birth controls pills and had high fat intake while a lower proportion breast fed, used HRT, alcohol, cigarettes or caffeine. The average age of diagnosis was significantly lower in AAW, with 16% diagnosed under age 40 compared to 4% of CW. Tumors from AAW more frequently had the triple negative phenotype (ER, PR, and HER-2/neu negative), and positive lymph nodes. The mortality rate was significantly higher in AAW (6%) compared to CW (1.5%). Conclusions: Despite the provision of standardized health care, high rates of screening mammograms and BSE, tumors from AAW are associated with poor prognosis and higher mortality rates. Although environmental components may influence tumor growth, the young age of onset and aggressive pathological characteristics described here suggest that aggressive tumor phenotype and outcome are reflective of population-specific molecular and biological differences.

P16

Mastectomy Rates in Urban Populations versus Rural Populations L. Jacobs,* K.A. Kelley, G.D. Rosson, M. Detrani, D.C. Chang. *Surgery, Johns Hopkins University, Baltimore, MD.*

Introduction Using the 2006 Surveillance, Epidemiology, and End Results (SEER) database linked to the 2004 Area Resource File (ARF), mastectomy rates in urban versus rural populations are examined. County and patient level data are evaluated for impact on mastectomy rates. Variables included age, stage, race, marital status, income, employment, and radiation facility staff density. The difference in the urban and rural mastectomy rates and the impact of the different variables on the receipt of mastectomies are reported. Methods This retrospective analysis of a combined dataset of variables from the 2006 SEER database and the 2004 ARF linked using the FIPS state county variable (National Bureau of Standards, U.S. Department of Commerce) evaluates multiple patient and county variables with multivariate regression. We hypothesize that rural mastectomy rates are higher than urban rates and that community level factors play a significant role in the treatment decisions. Results From 1992 to 2003, 126,205 patients that met the inclusion and exclusion criteria are recorded in the SEER database. The rural population (county population of > 20,000) comprised 9.61 % overall and 50.19% of those received a mastectomy. Multivariate analysis determined that rural residency of a patient increased the likelihood of mastectomy. Stage at diagnosis largely affected the receipt of mastectomy as expected. Other significant factors increasing likelihood of mastectomy included races other than white or black, widowed marital status, and the education level of the community where the patient resides. Finally, the likelihood of receiving a mastectomy increased with a smaller density of radiation technologists in the community. Data is available in the table attached. Conclusions This study is distinct from other studies in that it attempts to link patient factors from SEER to community levels factors from ARF. This study supports previous studies suggesting that the stage and location of radiation facilities effects mastectomy outcome; however, it differs from other studies in that age was not a significant factor which could have been controlled for by marital status.

Multi-variate analysis of mastectomy outcome

	Adjusting by density per population		
	Odds Ratio	95% Confidence Interval	P-value
Rural	1.46	1.17-1.83	.001
Age: 18-24			
25-29	0.82	0.38-1.76	n.s.
30-34	0.86	0.40-1.85	n.s.
35-39	0.87	0.40-1.87	n.s.
40-44	0.72	0.34-1.50	n.s.
45-49	0.69	0.33-1.47	n.s.
50-54	0.61	0.29-1.29	n.s.
55-60	0.66	0.31-1.37	n.s.
60-64	0.67	0.32-1.41	n.s.
65-69	0.75	0.36-1.59	n.s.
70-74	0.83	0.39-1.77	n.s.
75-79	0.96	0.45 -2.05	n.s.
80-84	1.11	0.51-2.42	n.s.
85-89	1.10	0.50-2.43	n.s.
90 and over	0.75	0.36-1.57	n.s.
Race: White			
Black	0.93	0.83-1.04	n.s.
Other	1.24	1.06-1.45	0.007
Stage: I			
II	2.26	2.18-2.35	0.00
III	11.34	9.96-12.90	0.00
Marital Status: Married			
Single	0.97	0.90-1.04	n.s.
Separated / Divorced	1.00	0.94-1.06	n.s.
Widowed	1.13	1.08-1.18	0.00
County-level factors			
Income: <30,000			
30,000 - 50,000	1.04	0.69-1.58	n.s.
>50,000	0.90	0.58-1.38	n.s.
Percent Employed	1.02	1.01-1.04	n.s.
Percent with HIgh school education or more	0.96	0.95-0.98	0.00
Density of radiation oncologist - per land area	1.00	0.99-1.00	n.s.
Density of radiation technologists - per land area	1.00	0.99-1.00	0.006

P17

Surgical treatment of liver metastases due to breast cancer
S. Nikolic,* M. Inic, A. Martinovic, M. Kocic, M. Marjanovic, M. Zegarac, I. Djurisic. *Clinic for oncology surgey, Institute for oncology and radiology of serbia, Belgrade, Serbia.*

Introduction In small number of patients liver is the only metastatic spot.Patients with solitary hepatic metastases have average survival of 6-14 months. In selected group of patients in which we could perform an adequate surgical procedure three year survival is 50 % and five year survival is 34%. Patients and Methods During the period of 2001 to 2005 we operated on 27 patients with hepatic metastases due to breast cancer. Decision to perform a surgical treatment was made by the multidisciplinary team who deals with breast cancer. We performed intraoperative ultrasound as well. The average age of our patients was 52. Tumor stage (pT) was pT1-29.4% and pT2 and upper stages-70.6%. Ductal carcinoma had 64.7% and lobular carcinoma had 35.3% of our patients. The number of axillary metastatic lymph nodes ranged from 0 (29.4%) to 8(11%). Preoperative hormone treatment was administered to all our patients. Positive estrogen receptor (ER+) had 70.6% and positive progesterone receptor (PR+) had 58% of patients. Neo adjuvant therapy was applied in 23.5% and systemic chemo therapy in 88.2% of patients. Results In two patients we performed breast surgery and liver resection in one act. We performed liver resection in 70.5% and ablation in 29.5% of cases. Resection of two or more segments was performed in 59% of patients. All patients had R0 resection. Two year survival was 71% and 29% died due to relapse. On patients who had liver resection has relapse in liver and is currently undergoing chemotherapy. Age of a patient, tumor type, the number of positive regional lymph nodes and the type of breast surgery does not affect survival of patients. Hormone receptor status is the only statistically valuable survival prognostic factor. We observed no postoperative mortality. Four patients were febrile in postoperative course and were treated conservatively. Conclusion Although very rare, metastases in liver could be the only metastatic spot of breast cancer. If there is a good control of a primary breast cancer and in the absence of an extra hepatic disease, surgical treatment should be proposed and eventually performed. Decision of the type of treatment should be made by the multidisciplinary team.

P18

Surgical Site Infection (SSI) After Breast Surgery: How Good is the CDC Definition? A.D. Throckmorton,* S.Y. Boostrom, T.L. Hoskin, S. Zakaria, J.H. Donohue, S. Sterioff, L.M. Baddour, J.C. Boughey, A.C. Degnim. *Surgery, Mayo Clinic - Rochester, Rochester, MN.*

Introduction: SSI rates after breast operations range from 1-29%. According to the Centers for Disease Control (CDC) and Prevention definition of SSI, the physician's clinical diagnosis of SSI is one criterion to satisfy the case definition but is subjective. The aims of present study were to characterize SSI after breast operations and to determine the rates of SSI defined by each CDC criterion. Methods: A retrospective chart review of 237 patients with methylene blue mapping between 1/2005 and 6/2006 who underwent 276 operations comprised the study group. SSI was defined based on CDC criteria of purulent drainage, presence of cellulitis, or physician concern of infection treated with antibiotics within 30 days of surgery. SSI rates were analyzed using the chi-square test. Results: In the cohort of 237 patients, 41 patients (17%) experienced SSI in 44/276 (15.9%) breast operations based on criteria including all patients treated with antibiotics. SSI rates do not vary significantly by procedure (Table 1). In 44 cases, 26 (59%) were treated with oral antibiotics for possible cellulitis, 14 (32%) had definite cellulitis, two (4.5%) had purulent drainage, and two (4.5%) were treated with antibiotics by referring physician. If SSI rates are restricted to groups with definite cellulitis or purulent drainage, the rates are reduced by almost two-thirds (Table 1). The median time to SSI diagnosis was 9 days (range 2-27), with 33/44 (75%) of SSIs occurring within the first 14 days after surgery. 15 cultures were obtained from various sources: 9 percutaneous aspirates, four cultures of drain fluid or exit site, and two swabs from wounds. Ten of 15 cultures were negative. The 5 positive cultures grew one or more of the following: Staphylococcus aureus, Enterobacter species, enterococci and Micrococcus species. Treatment for SSI included oral antibiotics alone in 40 cases (91%), intravenous (IV) antibiotics in two (4.5%), and IV antibiotics with debridement in two (4.5%). Conclusions: A provider's decision to treat possible cellulitis is a soft criterion of SSI that may overestimate the true SSI rate. Among patients with hard evidence of infection, culture results have limited value.

SSI Rates by Operation*

Operation	Total number	Treated unseen	Possible cellulitis	Definite cellulitis	Purulent drainage	Overall SSI rate (%)	Restricted Rate** (%)
BCT+SLNB	95	0	8	4	0	12.6	4.2
BCT+ALND	19	1	0	2	0	15.8	10.5
TM/TM+SLNB	134	1	14	6	2	17.2	6.0
MRM	28	0	4	2	0	21.4	7.1
All	276	2	26	14	2	15.9	5.8

*Abbrev: BCT (breast conservation therapy), SLNB (sentinel lymph node biopsy), ALND (axillary lymph node dissection), TM (total mastectomy), MRM (modified radical mastectomy)
** Restricted SSI rate reflects only those patients with hard clinical evidence (definite cellulitis or purulent drainage) of SSI

P19

Predictors of Re-excision Among Women Undergoing Breast Conserving Surgery for Cancer J. Waljee,* E.S. Hu, L.A. Newman, A.K. Alderman. *University of Michigan, Ann Arbor, MI.*

Background: Up to 60% of breast cancer patients who undergo breast conserving surgery (BCS) require re-excision to obtain clear margins, causing delays in adjuvant treatment and poor aesthetic results. However, patient and treatment-related factors associated with re-excision are not well defined. Methods: We surveyed all women undergoing breast conserving surgery between January 2002 and May 2006 regarding their breast disease (n=714, response

rate=79.5%). The medical record was reviewed to determine the receipt of re-excision lumpectomy following BCS, and to obtain tumor stage, histology, and biopsy method (surgical vs. needle biopsy). Patient age, breast size, tumor location in the breast, and receipt of chemotherapy were self-reported. Logistic regression was used to determine significant predictors of re-excision lumpectomy. Results: In this sample, 49.7% of patients required re-excision. The majority of women requiring re-excision required 2 excisions (43.1%), and 6.6% required 3 excisions. Factors significantly correlated with re-excision lumpectomy included smaller breast size (A cup: OR=2.7; 95%CI: 1.32-5.52; B cup: 1.63; 95%CI: 1.02-2.62), lobular histology (OR=1.93; 95%CI: 1.15-3.25), and receipt of surgical biopsy (OR=3.35; 95%CI: 2.24-5.02). Women who received adjuvant chemotherapy (OR=2.49; 95%CI: 1.19-5.22) were more likely to require re-excision compared with women who received neoadjuvant chemotherapy. Conclusions: Re-excision lumpectomy is common, and is significantly correlated with smaller breast size, lobular histology, surgical biopsy, and chemotherapy timing. Attention to these risk factors can improve the quality of care delivered to BCS patients by decreasing the cost and morbidity associated with multiple re-excision procedures.

P20

Factors Associated with Lymph Node Assessment in DCIS: Analysis of 1988-2002 SEER Data M.R. Porembka,[1]* R.L. Abraham,[2] J.A. Sefko,[2] A.D. Deshpande,[2] D.B. Jeffe,[3] J.A. Margenthaler.[1]
1. Department of Surgery, Washington University School of Medicine, St. Louis, MO; 2. Department of Community Health, Saint Louis University School of Public Health, St. Louis, MO; 3. Department of Medicine, Washington University School of Medicine, St. Louis, MO.

INTRODUCTION: Ductal carcinoma in situ (DCIS) represents 20-30% of mammographically detected breast cancers. Because core needle biopsy possesses an inherent sampling error that can underestimate invasive disease, the role of lymph node assessment (LNA) in women with DCIS remains unclear. The goal of this study was to identify factors that motivate surgeons to perform LNA in patients with DCIS. METHODS: Using the 1988-2002 Surveillance, Epidemiology, and End Results (SEER) Program data, we conducted a retrospective, case-control study to identify variables associated with LNA in DCIS patients. Specifically, the use of axillary lymph node dissection (ALND) was compared with sentinel lymph node biopsy (SLNB). Multivariable logistic regression models identified patient and tumor-related factors associated with the utilization of LNA and with the method of LNA performed (recorded only in 1998-2002). We report adjusted odds ratios (aOR) and 95% confidence intervals (CI). RESULTS: Of 23,502 women diagnosed with DCIS (mean age 58 yrs, range 18-99), LNA was performed in 6,650 (28%) cases (37% underwent mastectomy, while 63% had breast conservation therapy [BCT]). Median tumor size was 7.0 mm. Factors associated with LNA included age younger than 80 years (aOR 1.47; CI 1.24-1.75), use of mastectomy (aOR 11.06; CI 10.30-11.90), tumor size > 9 mm (aOR range 1.27-1.97 for 10-mm increments from 10 to ≥ 50 mm), and poorly differentiated grade (aOR 1.33; CI 1.11-1.55). From 1998 to 2002 (when data related to the method of LNA was available), 10,637 women underwent resection for DCIS (73% mastectomy; 26% BCT); of these, 2,219 (21%) had concurrent LNA. For women who had BCT, 33% had SLNB and 67% had ALND. For women who had mastectomy, 13% had SLNB and 87% had ALND. In the multivariable model, women who had mastectomy were 3.52 times more likely to receive ALND (CI 2.71-4.57) compared with SLNB. CONCLUSION: Optimal guidelines for the use of LNA in DCIS are yet to be defined. However, from 1998-2002, there appeared to be a persistent, and perhaps excessive, use of ALND for LNA in women with DCIS.

P21

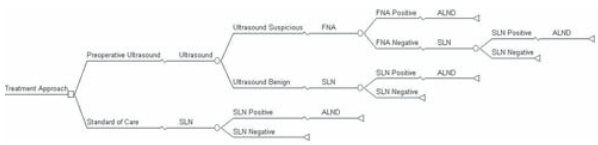
Breast Conserving Surgery Use Among California Latinas L.M. Guirguis,[1]* K.R. Bauer,[2] C.A. Parise,[3] M. Brown.[2] *1. Surgical Oncology, Sutter Cancer Center, Sacramento, CA; 2. Public Health Institute/California Cancer Registry, Sacramento, CA; 3. Sutter Institute for Medical Research, Sacramento, CA.*

Introduction. In the state California there is an apparent under utilization of breast conserving surgery (BCS) among Hispanic women with breast cancer compared to non-Hispanic white women (NHW). We conducted a review of the California Cancer Registry (CCR) examining demographic and tumor factors to explore the difference between the rates of BCS and mastectomy among Hispanic women. Methods. Prospectively collected data from the CCR was used to identify Hispanic (n=14,005) and NHW (n=71,610) women who underwent surgery for breast cancer from 2000-2004. Demographic factors including ethnicity, age, rurality, socioeconomic (SES), marital, and insurance status, and tumor characteristics including stage, grade, nodal status, phenotype and size were examined among these two groups of women. Results. Fifty-two percent of Hispanic women underwent BCS compared with 57 % of NHW ($p<0.0001$). Hispanic women presented with breast cancer at an earlier median age (55 versus 63, $p<0.0001$), with larger tumor size (3.0cm versus 1.6cm, $p<0.0001$), and more often demonstrated the triple negative phenotype (10.5% versus 7.2%, $p<0.0001$), as well as nodal positivity (37.5% versus 29.2%, $p<0.0001$). Logistic regression analysis, however, did not demonstrate a statistically significant decrease in the odds of Hispanic women having BCS (OR=0.98, 95%CI= 0.94-1.03). All women aged 75+ (OR=0.73, 95%CI= 0.68-0.77), in the lowest SES (OR=0.69,95%CI= 0.65-0.74), having public insurance (OR=0.91, 95%CI= 0.88-0.96), with tumor size 2.1-5.0 cm (OR=0.56, 95%CI= 0.52-0.59), and node positivity (OR=0.65, 95%CI= 0.61-0.68) were less likely to have BCS. Conclusions. Breast conserving surgery among Hispanic women in the state of California is not used as extensively as among NHW. When demographic factors and tumor characteristics are taken into account ethnicity alone does not predict surgical therapy. Older women, those in the lowest SES with public insurance and larger aggressive tumors are less likely to receive BCS. The proportion of Hispanic women presenting with features predicting poor BCS use is higher than among NHW.

P22

Cost Modeling of Preoperative Axillary Ultrasound and Fine Needle Aspiration to Guide Surgery for Invasive Breast Cancer J.C. Boughey,[1]* J.P. Moriarty,[2] J.S. Egginton,[2] A.C. Degnim,[1] M.S. Gregg,[2] K. Hall Long.[2] *1. Surgery, Mayo Clinic, Rochester, MN; 2. Mayo Clinic, Rochester, MN.*

Introduction Preoperative axillary lymph node ultrasound (US) and fine needle aspiration (FNA) biopsy can identify some node positive patients and avoid sentinel lymph node (SLN) surgery. We sought to compare the incremental costs with and without preoperative US/FNA for invasive breast cancer. Methods Using decision analytic software we constructed a model to assess the costs associated with the two strategies as shown in the figure. The probabilities of test parameters were obtained from a comprehensive literature review. Costs were derived from Medicare payment rates and actual resource utilization. One-way, threshold, and probabilistic sensitivity analyses (using Monte Carlo simulation techniques) assessed uncertainty in model results. Results Based on the literature the following parameters were chosen: nodal metastases rate 40%, US sensitivity 64%, FNA sensitivity 65%. Baseline model results estimate total mean costs per patient of $11,736 with US/FNA and $11,856 without, an incremental cost savings of $120. Results were insensitive to assumed US and FNA costs but sensitive to SLN costs on one-way sensitivity analyses. US/FNA remained cost-saving even if SLN costs were up to 32% lower than baseline estimates. Probabilistic analyses showed an incremental mean cost savings of $118 per patient in favor of US/FNA (95% CI of cost difference: -$233 to -$13). Most (98.6%) simulations resulted in costs favoring the use of axillary US/FNA, with all the iterations having an estimated cost difference less than $41. The results of the model were robust to extremes of US sensitivity, FNA sensitivity, nodal metastases rates and US and FNA costs. As nodal positivity rate increases the cost-savings of US/FNA increases. US/FNA was cost saving for all tumor stages. The costs of the two strategies became equivalent at a nodal positivity rate of 19%. Conclusions The additional cost of performing axillary US on every patient and possible FNA is balanced by the savings from avoiding SLN in some patients. Routine use of preoperative axillary US with FNA to guide surgical planning may decrease the overall cost of patient care for invasive breast cancer.



P23

Lymphedema after Sentinel Node Biopsy: Do we have the Complete Picture? L. Kruper,[1]* L.G. Wilke,[2] A.E. Giuliano.[1] *1. John Wayne Cancer Institute, Santa Monica, CA; 2. Duke University, Durham, NC.*

Introduction: An important secondary outcome recently reported from three large randomized studies evaluating the use of sentinel lymph node biopsy (SLN) versus axillary node dissection (AXLND) is the rate of lymphedema. In the prospective American College of Surgeons (ACOSOG) Z0010 trial which is evaluating the prognostic significance of micrometastasis in sentinel lymph nodes an overall 6.9% rate of lymphedema has been published. We investigated the rate of lymphedema in our sub-population of Z0010 patients. Methods: Eligible patients included women with clinical T1/T2N0M0 breast cancer (n=408). There were no patients who failed sentinel node mapping. Patients who underwent a completion ALND (n=64, 15.7%) were excluded. 26 patients were lost to follow-up. Lymphedema rates were evaluable in 263 patients and determined by arm measurements at baseline and 6 months post-operatively. An increase of 2cm above baseline and in reference to the contralateral arm was used to determine the presence of lymphedema. Results: The patient characteristics of our population closely resembled those of the complete ACOSOG population. Our positive SLN rate was 23% compared to 24% ($p = 0.66$). 15.7% of our patients underwent ALND vs. 15% in ACOSOG ($p = .71$). The median BMI and age in our group were 23.6 and 55, respectively, vs. 26.4 and 56. Our average number of SLN was 2.1 compared to 2.3. In our sub-group, SLN biopsy was performed utilizing isosulfan blue only in 78.9% whereas ACOSOG reported a 14.7% rate ($p < .0001$). No patients received radiocolloid alone vs 5.7% in the ACOSOG group. The combination of blue dye and radiocolloid was used in 18.1% of our patients vs. 78.7%. The lymphedema rate was 0.8% as compared to 6.9% at 6 months in the ACOSOG report ($p < .0001$). The subjective rate of lymphedema (without increase in arm measurements) was 1.9%, and was not reported in the complete ACOSOG population. Conclusion: We examined demographic factors previously described to have been associated with an increased risk of lymphedema in patients after sentinel node biopsy. There may be SLN technique differences which explain this statistical difference in surgical outcomes.

P24

Targeting of the MYC-oncogene Inhibits Breast Cancer Molecular Markers and Growth Parameters In Vitro and In Vivo in a Chick Embryo Model for Tumor Growth B. Rymeski,[2]* D.S. Galileo,[3] V. Sampson,[1] N. Rong,[1] V. Aris,[4] P. Soteropoulos,[4] N.J. Petrelli,[5] S.P. Dunn,[1] L.J. Krueger.[1] *1. Department of Molecular Genetics, Cellular and Tissue Transplantation, A.I. duPont Hospital for Children, Wilmington, DE; 2. Department of Surgery, Christiana Care Health System, Newark, DE; 3. Department of Biological Sciences, University of Delaware, Newark, DE; 4. Center for Applied Genomics, Public Health Research Institute, of UMDNJ-New Jersey Medical School, International Center for Public Health, Newark, NJ; 5. Helen F. Graham Cancer Center, Christiana Care Health System, Newark, DE.*

Dysregulation of MYC oncogene is commonly found in breast cancer patients resulting in more frequent relapse and poorer survival. Using 10058-F4, a small molecular weight drug that inhibits MYC-MAX transcription, we studied two-breast cancer lines differing in metastatic potential. METHODS: MDA-MB-231 and -468 was studied using a MTT assay in drug-exposed cells. In silico analysis of gene expression results on Affymetrix microarrays was compared in these 2 lines. Real time Taqman-MGB technology PCR evaluated gene specific expression in exposed cells and extent of invasive and metastatic breast cancer cell colonization in our chick embryo in vivo model. Tumor localization in the chick brain, liver and lung was determined by histochemical and lacZ staining. G418 selection determined explanted surviving cancer colonies. RESULTS: 12,000 gene expression levels were compared using robust multi-array analysis (RMA) and only 6 genes showed either a 2-fold increase - decrease (231/468). i.e., LDH-B, PRG1, AXL, unknown; (up) and FOXA1 and RARRES1; (down). These changes may identify key pathways involved in the divergent phenotypes (Table I). Triplicate PCR analysis of MYC showed a 3.5-fold relative increase in 468 over 231 cells. Cells exposed to drug showed decreased cell growth (range 62-93 uM compound, $p<0.05$) by MTT in replicates e.g., control absorbance (562 nm) of 2.5+/-0.25 and 1.13+/- 0.08 and exposed (93 uM) of 1.43 +/-0.12 and 0.87+/-0.05, respectively, for 468 and 231 cells. 468 cells were 2.4-fold more sensitive to drug at 93 uM. This confirms results in Burkitt lymphoma where higher MYC lines showed a paradoxical greater response to MYC inhibition. Effects on MYC-MAX downstream targets were shown by PCR and independently confirmed in MYC-targeted siRNA results. Baseline colonization by breast cancer cells also was determined in the chick embryo model for comparison to ongoing experiments on the injection of drug treated breast cancer cells. CONCLUSIONS: We demonstrate down regulation of MYC results in an altered phenotype of metastatic and non-metastatic breast cancer lines in vitro and in vivo.

Phenotypic heterogeneity between MDA-MB 231 & MDA-MB 468

	[MYC]*	[Her2neu]*	[Bcl2]*	ER/PR receptor^	Ah responsive^	E-cadherin^	Vimentin^	Experimental mets^
MDA-MB 231	0.92	1.09	108.82	-	-	-	+	+
MDA-MB 468	3.49	1.83	105.33	-	+	+	-	-

* Relative concentrations determined by real-time TaqMan-MGB PCR normalized by rRNA

^ As reported by MD Anderson Cancer Center at http://www.mdanderson.org/departments/cancerbiology/dIndex.cfm?pn=31062032-B0EB-11D4-80FB00508B603A14

P25

Outcomes of Elderly Patients With Breast Cancer Receiving Standard and Non-Standard Therapy V. Velanovich.* *Surgery, Henry Ford Hospital, Detroit, MI.*

Background: Previous studies have documented that elderly patients with breast cancer are more frequently "under treated" compared to younger patients. Although there are medically sound reasons for the under treatment, the outcomes of this approach is not well documented. Hypothesis: Elderly patients who are under treated for breast cancer will not have a higher breast-cancer related mortality compared to patients who receive standard treatment. Patients and Methods: A random sample of patients >60 years old treated for breast cancer from January, 1993 to December, 1997 at our institution was selected. Data collected included year of diagnosis, age at diagnosis, race, number and type of comorbid conditions, stage, treatment, survival and cause of death. Treatment was judge as "standard" if it meet the National Comprehensive Cancer Network's guidelines for breast cancer based on type of tumor and stage for the years 1993 to 1997, inclusive. Results: There were 178 standard therapy patients (mean age 70 + 7 years) and 57 nonstandard therapy patients (mean age 77 + 9 years). Median number (with ranges) of co-morbidities was 1 (0-5) in the standard therapy group vs. 2 (0-6) in the non-standard therapy group. 12% of standard therapy patients were proven stage III or IV vs. 4% of the non-standard therapy group. Follow-up was from 0 to 162 months. 35% of standard therapy patients died vs. 44% of the non-standard therapy patients. Cause of death was breast-cancer related in 42% of the standard therapy patients vs. 32% of the non-standard therapy patients. Median survival of patients who died was 43.5 months in the standard therapy group compared to 68 months in the non-standard therapy group. Conclusions: Non-standard therapy patients had a higher number of co-morbidities, higher overall death rate, but fewer breast cancer related deaths. Standard therapy patients who died had a shorter median survival despite standard therapy.

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Strategies for optimizing pathologic staging of sentinel lymph nodes in breast cancer patients E.V. Madsen,[1]* J. Van Dalen,[2] J. Van Gorp,[3] I.H. Borel Rinkes,[4] T. Van Dalen.[1] *1. Diakonessenhuis - Department of Surgery, Utrecht, Netherlands; 2. RSM Erasmus University - Department of Information and Decision Sciences, Rotterdam, Netherlands; 3. Diakonessenhuis - Department of Pathology, Utrecht, Netherlands; 4. University Medical Center Utrecht - Department of Surgery, Utrecht, Netherlands.*

Introduction Due to the extensive pathologic evaluation of the sentinel lymph node (SLN) micrometastases are frequently observed since the introduction of the SLN-procedure in breast cancer patients. Assuming that micrometastases are clinically relevant the histopathologic examination of SLNs should be sensitive enough to detect them. The probability of detecting micrometastases was calculated when examining the SLN according to the current Dutch pathology

protocol and strategies were evaluated to optimize the chance of detection. Patients and methods The dimensions of twenty consecutive axillary SLNs in patients with cT1-2N0 breast cancer were measured. In a mathematical model the probability of detecting micrometastases (TNM-stage N1mi) in a SLN was calculated given standard examination of the SLN according to the national pathology guideline, i.e. bisecting the SLN, and examining three levels from both slices at 250µm intervals. Similarly, strategies to optimize the probability of detecting micrometastases were explored. Results The median volume of a SLN was 0.8 cm3 (range 0.3 – 3.45). The dimensions of the median sized SLN were: length 15mm, width 10mm and height 10mm. When applying the pathology guidelines, the calculated probability to detect a micrometastasis was 18% for a 200µm micrometastasis and 69% for a 2.0mm metastasis (table 1). To detect the smallest micrometastasis in a median sized SLN with a 95% probability, the interval between the sections must be decreased to 200 instead of 250µm and twenty levels from both halves must be examined. Sectioning and examining SLNs at 2mm intervals, as proposed for SLNs thicker than 10mm, would result in a 100% probability of finding 2mm micrometastases in the largest SLN, but at the expense of a lower chance of detecting 200µm micrometastases (11% instead of 15%). Conclusion Given a prognostic significance of TNM-stage N1mi, our current pathology guidelines are not sensitive enough. The number of sections should be increased considerably, while the interval between the examined cuts should be no more than 200µm.

Probability of detecting micrometastases (TNM stage N1mi) using the current Dutch pathology guidelines

	Pdetect micrometastasis	
	smallest micrometastasis 200µm	largest micrometastasis 2mm
volume and measures of the SLN		
median SLN 0.8 cm^3; 15mm x 10mm x 10mm	0.18	0.69
smallest SLN 0.3 cm^3; 10mm x 7mm x 5mm	0.36	1.0
largest SLN 3.45 cm^3; 25mm x 20mm x 12mm	0.15	0.59
	0.11*	1.0*

* when examined according to the examination protocol for SLNs thicker than 10mm.

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Preliminary Results of a Pilot Study of Circulating Tumor Cells in Patients Undergoing Surgery for Primary Breast Cancer N. Thepjatri,[2]* J.A. Kuhn,[1] S.M. Knox,[1] M.D. Grant,[1] J.J. Nemunaitis,[1] T.L. Fisher,[1] J.P. Lamont.[1] *1. Baylor University Medical Center, Dallas, TX; 2. Midwest Breast Center, Indianapolis, IN.*

Introduction: Circulating Tumor Cells (CTCs) have recently been shown to be an independent predictor of progression-free and overall survival in patients undergoing treatment for metastatic breast cancer. This study evaluates the presence and significance of CTCs in patients undergoing surgical resection of clinically localized primary breast cancer. Methods: Patients undergoing surgery for clinically localized primary breast cancer were enrolled in this prospective study. Four 7.5 cc vials of peripheral blood (total volume 30 cc) were drawn pre-operatively (PreOp) and at 2 weeks post-operatively (PostOp). The samples were centrifuged and the sera combined to a final volume of 7.5 cc, and the CellSearch (Veridex, LLC) system was used to identify circulating epithelial cells. Data was collected on other prognostic factors including tumor size, grade, hormonal receptor status, proliferative index, HER-2 expression, and regional lymph node involvement. Results: Thirty patients with primary breast cancer were enrolled at a single tertiary referral center. The mean age was 60. Primary tumor size was <2cm (n=9), 2-5cm (n=19), and >5cm (n=2). Ten patients (33%) had detectable CTCs PreOp, with the mean number of CTCs found being 1.3 (range 0-21). Twenty-two patients had blood drawn PostOp and 8 (36%) were found to have CTCs. Three of these patients had positive CTCs both PreOp and PostOp while 5 had detectable CTCs only in the PostOp specimen. Overall, 15 patients (50%) were found to have CTCs either PreOp or PostOp. Based on T stage, the likelihood of any detectible CTCs was T1: 45%, T2: 50%, and T3: 100%. Based on N stage, the likelihood CTC detection was N0: 35%, N1 or greater: 69%. Conclusions: This preliminary data suggests that CTCs are detected in breast surgery patients 50% of the time. The likelihood of detecting CTCs doesn't appear to correlate with T stage, but does appear to correlate with pathologically positive nodes. Further study will allow correlation with other pathological variables. Long term clinical follow up is required to determine the clinical significance of CTCs in patients undergoing breast surgery.

P28

Environmental factors and breast cancer risk: analysis of organochlorine and polychlorinated biphenyls in human breast tissue and serum S.M. Feldman,[1]* R. McNally,[2] P. Klein,[2] P. Friedmann,[1] S. Im,[4] N. Nugent,[1] H. Nemiroff,[2] S. Boolbol,[1] R. Jansing.[3] *1. Breast Surgical Oncology, Beth Israel Medical Centerr, New York, NY; 2. Benedictine Hospital, Kingston, NY; 3. Wadsworth State Lab, Albany, NY; 4. Albert Einstein College of Medicine, Bronx, NY.*

Background: Environmental pollutants are likely a risk factor for developing breast cancer. Prior studies analyzing serum levels of organochlorines and polychlorinated biphenyls(PCBs) have not demonstrated elevated levels in breast cancer patients. This IRB approved study was undertaken to compare levels of these substances in serum and tissue for patients with breast cancer and benign breast disease. The study participants were located in the Hudson river valley in New York. Methods: Study design involved a nonrandomized, prospective case-control of 101 women undergoing breast surgery. 75 had a diagnosis of breast cancer and 26 patients with benign disease. Serum and fatty breast tissue (1 gram) were collected from each patient for analysis. This included a panel of 15 organochlorine pesticides and 30 PCB congeners analysed using mass spectroscopy . Statistical analysis was performed using the spearman correlation coefficient and non-parametric Wilcoxon rank test. Results: Analysis of the correlation data between serum and tissue showed a non significacnt correlation for oxychlordane and mirex (r=0.12, p=0.25). There was a low correlation (r=0.23, p=0.025) for DDT . The other compounds had medium or high correlation. This suggests that serum levels may not accurately reflect tissue levels for certain environmental contaminants. Comparison of levels for breast cancer patients vs. benign disease showed significantly higher levels of tissue PCB congeners IUPAC 118,138,153,180 and DDE (p=0.049) in breast cancer patients. Serum levels of IUPAC 153, HCH and DDE (p=0.08) were higher in breast cancer patients. Discussion: This study suggests that chlorinated pesticides and PCBs may have a role in breast carcinogenesis. Prior studies have not demonstrated increased serum levels of PCB's or organonchlorine pesticides in breast cancer patients compared to controls. This study suggests that serum levels may not accurately reflect the breast tissue exposure. A larger muliticenter study involving patients with more diverse environmental exposures will be helpful.

P29

The genomic heritage of lymph node metastases: implications for clinical management of patients with breast cancer D.L. Ellsworth,[1] R. Ellsworth,[1]* T.E. Becker,[2] B. Deyarmin,[1] H.L. Patney,[1] J.A. Hooke,[2] C.D. Shriver.[2] *1. Windber Research Institute, Windber, PA; 2. Walter Reed Army Medical Center, Washington, DC.*

Background: Metastatic breast cancer is an aggressive disease associated with recurrence and decreased survival. To better understand how genomic alterations in axillary lymph node metastases may affect outcome in breast cancer patients, we used allelic imbalance (AI) to determine the molecular heritage of primary breast tumors and corresponding regional metastases in 35 patients with node-positive breast cancer involving multiple axillary nodes. Methods: Pathologically positive nodes were identified by H&E histology and immunohistochemistry. Primary breast tumors and matched metastases were isolated from paraffin-embedded samples by laser-assisted microdissection. AI was assessed at 26 chromosomal regions and used to examine the timing and molecular mechanisms of metastatic spread. Hierarchical clustering assessed overall differences in patterns of AI and phylogenetic analysis inferred the molecular heritage of axillary lymph node metastases. Results: Overall AI frequencies were significantly higher ($p<0.05$) in primary breast tumors compared to lymph node metastases. Genetically divergent lineages of metastatic tumors appeared to independently colonize the axillary lymph nodes, suggesting that multiple molecular mechanisms may govern the process of metastasis in individual patients. Progenitor cells for some metastases appeared to acquire metastatic potential early in the disease process and progressed with

few genomic alterations, while other metastases may have developed later and harbored many chromosomal alterations. Conclusions: Axillary lymph node metastases are genetically diverse and appear to arise at different times during disease progression. Genomic diversity among metastases and the timing of metastatic nodal spread may be associated with response to adjuvant therapy, recurrence, and survival, and thus may be important to improving clinical management of breast cancer patients.

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A contemporary, population-based study of lymphedema risk factors in older breast cancer women T.W. Yen,* X. Fan, P.W. Laud, A.P. Walker, A.B. Nattinger. *Surgery, Medical College of Wisconsin, Milwaukee, WI.*

INTRODUCTION: The clinical epidemiology of lymphedema (LE) remains poorly understood. The aim of this study was to identify potential risk factors for LE in a contemporary, unselected population of older breast cancer patients. METHODS: Women (65-89 years) from Illinois were identified from Medicare claims as having initial breast cancer surgery in 2003. Two telephone surveys were conducted by a median of 39 months postoperatively. Women were classified as having LE if they: 1) were told by a doctor that they had LE or 2) reported ipsilateral arm swelling that was absent on the contralateral arm. Type of surgery and pathology information were obtained from Medicare claims and the Illinois state cancer registry. RESULTS: Of the 481 patients operated on by 271 surgeons throughout Illinois, 30% underwent sentinel lymph node biopsy (SLNB) and 50% axillary lymph node dissection (ALND). At a median of 39 months postoperatively, 59 (12.3%) had LE. Among the 146 patients who underwent SLNB, a median of 2 (range: 0 to 15) lymph nodes (LNs) were evaluated and 6 (4%) patients developed LE. Among the 238 patients who underwent ALND, a median of 9 (range: 0 to 31) LNs were evaluated and 50 (21%) patients developed LE. Age, race, tumor size, and receipt of radiation or hormonal therapy were not associated with LE. On multivariate analysis (Table), when controlling for all other variables, the independent predictors of LE were the presence of LN metastases, ALND approach and the removal of an increasing number of LNs. CONCLUSIONS: Twelve percent of a contemporary, population-based cohort of elderly breast cancer survivors have self-reported LE three years postoperatively. In contrast to older literature suggesting an independent effect of radiation therapy on LE development, we failed to find such an effect. In this unselected group of predominately community-based surgeons, women who undergo SLNB, compared to ALND, have a substantially decreased risk of developing LE. A sufficient number of LNs should be removed to accurately determine LN status. However, even when SLNB is performed, the removal of each additional LN is associated with a 9% increased odds of developing LE.

Variables associated with lymphedema development in multivariate logistic regression analysis for breast cancer survivors (n = 481)

Variable	Category	Odds Ratio	95% CI	p-values
Lymph node metastasis				<0.0001
	No Yes	1.0 14.43	4.58 - 45.47	
Axillary surgery				0.03
	SLNB ALND No axillary surgery	1.0 3.02 1.33	1.14 - 8.03 0.30 - 5.80	
No. of lymph nodes removed		1.09*	1.02 - 1.17	0.01

* Odds ratio and confidence intervals (CI) reflect the risk of developing lymphedema per each additional lymph node removed.

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Neoadjuvant Chemotherapy Decreases the need for Re-excision of Breast Cancers between 2 and 4 cm Diameter C. Christy,* B. Grube, D. Black, M. Abu-Khalaf, G. Chung, M. DiGiovanna, S. Higgins, J. Weidhaas, L. Harris, D. Lannin. *Surgical Oncology - Breast Surgery, Yale University, New Haven, CT.*

INTRODUCTION: It is well accepted that neoadjuvant chemotherapy can result in increased breast preservation for breast cancers greater than 4 cm in size. The benefits of neoadjuvant chemotherapy are less clear, however, for patients who present with smaller tumors and are already candidates for breast-preserving surgery. The goal of this study is to assess the effect of neoadjuvant chemotherapy on breast cancers between 2 and 4 cm diameter. METHODS: A retrospective chart review was conducted of patients diagnosed with new invasive breast cancer at a single Breast Center between the years 2002 – 2007. Patients were included in the study if their breast cancer was between 2 and 4 cm and their initial surgical treatment had been completed. Patients with distant metastases were excluded from the study. RESULTS: There were 133 new cancers that met the study requirements. Thirty-eight patients underwent neoadjuvant chemotherapy, and 95 patients had their surgery first, usually followed by chemotherapy. The two groups were similar except that the neoadjuvant patients were somewhat younger (mean age 50 vs 57, p< .01) and had slightly larger tumors (mean diameter 3.2 vs. 2.8 cm, p< .01). The initial surgery was lumpectomy for 25 out of 38 patients (66%) in the neoadjuvant group compared to 55 out of 95 patients (58%) in the surgery group. For patients with lumpectomies, 2 out of 25 patients (8%) in the neoadjuvant group had positive margins and required re-excision (1 wider lumpectomy and 1 mastectomy) compared to 18 out of 55 patients (33%) in the surgery group (9 wider lumpectomy and 9 mastectomy), (p<.01). CONCLUSIONS: For tumors between 2 and 4 cm, neoadjuvant chemotherapy significantly decreases the need for re-excision following lumpectomy. This not only results in fewer mastectomies, but also avoids the morbidity and inferior cosmetic results associated with a re-excision lumpectomy.

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Assessment of Intraoperative Margin Status Using a Novel Device Measuring Surface Cellular Electromagnetic Properties E. Feldman,[1]* J. Woodward,[2] M. Gittleman,[3] J. Chiadis,[4] D. Hershko,[5] Z. Cheng,[1] L. Tafra.[1] *1. Department of Breast Surgery, Anne Arundel Medical Center, Washington, DC; 2. Department of Pathology, Anne Arundel Medical Center, Washington, DC; 3. Breast Care Specialists O.C., Allentown, PA; 4. Valley Pathology Associates, Allentown, PA; 5. Department of Surgery, Rambam Medical Center, Haifa, Israel.*

Background: Obtaining clear margins with a single procedure remains a challenge in breast conserving therapy. We sought to assess the performance of a handheld device which identifies electromagnetic differences between malignant and normal breast tissue at lumpectomy margins. Methods: Patients were enrolled in an ongoing multicenter prospective trial designed to evaluate the probe's performance. Measurements from surfaces of fresh intact lumpectomy specimens were taken intraoperatively and marked with pins. Surgeons were blinded to probe results. A corresponding 7mm wide specimen for each measurement site was examined by a pathologist. Probe readings were analyzed and compared to final histology. Results: Data was analyzed on a per-point, per-margin, and per-patient basis. Device measurements of 1065 points were compared to histological analysis from 89 patients on a per-point basis. In addition, 382/534 (71.5%) margins from 89 patients were analyzed on a per-margin basis. Histological examination of margins revealed 84/382(22%) to be positive and 298/382 (78%) as negative. The per-margin sensitivity and specificity of the device were 63% (95% CI: 52-73) and 65.5% (95% CI: 60-71). The margin sensitivity and specificity were higher than the point per-point values at 42.8 and 76.3%, respectively. The per-margin positive and negative predictive values of the probe were 34 and 86%, respectively. We also analyzed a mean of 4 margins per specimen of 75 patients from 2 institutions on a per-patient basis. 48 of 75 (64%) initial specimens had positive margins on final pathological evaluation. These included 7/48 (14.6%) addressed by the surgeon during the initial procedure. The probe detected all positive margins in the specimens of 20/48 (41.7%) patients. If device measurements had been used in conjunction with surgeons' estimation, 16 patients could have undergone complete excision during the primary procedure, totaling 23/48(48%)patients. Conclusions: When used in conjunction with surgical judgment, this device may significantly enhance the ability of surgeons to identify and re-excise positive margins during the initial procedure.

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Determinants of Breast Conservation Rates: Reasons for Mastectomy at a Comprehensive Cancer Center M.C. Lee,* K.A. Griffith, K. Rogers, V.M. Cimmino, K.M. Diehl, A.E. Chang, L.A. Newman, M.S. Sabel. *Surgical Oncology, University of Michigan, Ann Arbor, MI.*

Introduction: Bias in referral patterns and practice may impact breast conservation (BCT) rates between hospitals despite an aggressive use of BCT.

Retrospective studies of BCT rates are limited by their inability to differentiate indicated mastectomies (MAST) versus those chosen by the patient. Methods: Our prospective breast cancer database was queried for patients with invasive breast cancer who underwent surgical therapy at the University of Michigan over a 3-year period. Demographics, stage and histology were recorded along with the reason MAST was performed, categorized as "by need" (contraindication to BCT) or "by choice." Multivariate analysis was used to identify factors significantly associated with MAST by choice. Results: Of 784 patients, our BCT rate was 63%. 66% were felt to be good candidates for BCT on initial evaluation and with neoadjuvant chemotherapy (NeoCTX) over 80% went on to successful BCT. 15% chose to undergo MAST, and failed attempts to achieve negative margins resulted in MAST in 5% of patients. Of the 34% of patients felt to be poor candidates for BCT, it was absolutely contraindicated in 44%, while 56% were thought to have a tumor-to-breast size ratio too large for successful BCT. Of these patients, 80% underwent NeoCTX in an attempt to downstage the primary tumor and perform BCT, successful in 52%. Without the use of NeoCTX, our BCT rate would have been only 53%. BCT was associated with tumor size, histology and nodal status, but not older age, either by choice or by need. Age under 40 had a higher MAST rate, driven largely by prophylaxis. Lobular pathology was associated with an increased rate of mastectomy due to multicentricity, but not failed attempts at BCT. Conclusions: At our cancer center, BCT rates are driven more by contrainidcations than patient choice, and may be heavily skewed towards mastectomy due to referral patterns. Besides tumor stage and histology, BCT rate will be dramatically impacted by NeoCTX or genetic counseling. Examining BCT rates alone as a measure of quality, therefore, is not an appropriate standard across institutions serving diverse populations.

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Cost Analysis of the American Cancer Society (ACS) Guidelines for Breast Screening with MRI: An Alternative Strategy versus the 20% Solution C.D. Murphy,[1]* J.M. Lee,[1] B. Drohan,[2] C.J. Lawrence,[1] D.B. Kopans,[1] R.H. Moore,[1] S.H. Javid,[1] M.A. Gadd,[1] M.C. Specht,[1] K.S. Hughes.[1] *1. Surgery, Massachusetts General Hospital, Boston, MA; 2. University of Massachusetts Lowell, Lowell, MA.*

Introduction: The ACS suggests that women with ≥20% lifetime risk of breast cancer (lifetime risk) should undergo screening MRI. These guidelines exclude a large number of high risk women with ≥10% risk of BRCA1/2 mutation but <20% lifetime risk. The goals of this analysis were to determine the number of mutation carriers in a screening mammography population, and to compare costs of ACS guidelines to alternative screening strategies using genetic testing followed by MRI limited to mutation carriers (selective MRI). **Methods:** Family histories (age, cancer, Ashkenazi ethnicity) of 18,190 patients undergoing screening mammography from 2003-2005 were analyzed. BRCAPRO was used to identify patients in two groups (1: ≥20% lifetime risk, 2: ≥10% risk of mutation but <20% lifetime risk) and to determine the expected number of mutation carriers in each. Data was scaled to a population of 10,000. Ten year cost of MRI (Medicare reimbursement) was compared to cost of genetic testing (Myriad) plus selective MRI. **Results:** For an extrapolated 10,000 women, 43 have ≥20% lifetime risk of which 14 are predicted mutation carriers; 206 have ≥10% mutation risk but <20% lifetime risk, of which 35 are predicted mutation carriers. Following ACS criteria, screening costs for women with ≥20% lifetime risk are $552,120; for the same group genetic testing followed by selective MRI costs $276,220. Genetic testing and selective MRI for women with ≥10% risk of mutation but <20% lifetime risk costs $948,480, but identifies an additional 35 (71%) mutation carriers. **Conclusions:** Adding genetic testing to the ACS guidelines decreases cost by 50%. Expanding the ACS criteria to include patients with <20% lifetime risk but ≥10% mutation risk and including genetic testing adds upfront costs, but allows more accurate risk stratification and provides access to screening, chemoprevention and prophylactic surgery to many more mutation carriers. Until more data exists on MRI in high risk women who are not BRCA1/2 carriers, we recommend consideration of genetic testing and selective MRI for all women with ≥10% mutation risk.

Cost of MRI Screening and Genetic Testing of High Risk Patients

		ACS Approach	Alternative Strategy			
Risk Group	**n***	**10 Year Cost MRI Alone**	**Cost Genetic Testing**	**Predicted # Mutation Carriers**	**10 Year Cost MRI of Mutation Carriers**	**10 Year Cost Genetic Testing + MRI of Mutation Carriers**
>20% Lifetime Risk of Breast Cancer	43	**$552,120**				
>20% Lifetime Risk of Breast Cancer	43		$96,920	14	$179,760	**$276,220**
≥10% mutation risk and <20%Lifetime Risk of Breast Cancer	206		$499,080	35	$449,400	**$948,480**

*Based on screening population of 10,000 patients

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Correlation of COX-2 in Stage I-III Triple Receptor-Negative Breast Cancer K. Mosalpuria,* S. Krishnamurthy, M. Cristofanilli, I. Bedrosian, F. Meric-Bernstam, B. Singh, A. Lucci. *Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.*

OBJECTIVE: COX-2 expression in breast cancer has been associated with high grade tumors and worse overall outcome. We hypothesized that COX-2 expression in primary breast cancer is also associated with triple receptor-negative (TRN) status (tumors negative for ER, PgR, and HER2). METHODS: Clinical and pathological data were collected from 109 patients with Stage I-III breast cancer in a prospective study of primary tumor characteristics and micrometastatic disease in bone marrow and peripheral blood. COX-2 in primary tumor was determined using immunohistochemistry, and COX-2 positive status was defined as ≥5% of tumor cells staining positive. The CellSearch system (Veridex Corporation, Warren NJ) was used to detect circulating tumor cells (CTCs) in whole blood. CTCs were defined as nucleated cells lacking CD45 but expressing cytokeratins (CK) 8, 18, or 19. Presence of ≥1 epithelial cells per 10 mL of blood was considered positive for CTCs. Bone marrow (10ml each side) was obtained from bilateral iliac crests. Anti-CK antibody was used to identify disseminated tumor cells (DTCs) in bone marrow, with ≥1 CK staining cells considered positive. Primary tumor characteristics studied included: tumor size, ER, PgR, HER2, tumor grade, histological type, lymphovascular invasion (LVI), Ki-67 and lymph node metastases. Statistical analysis utilized Chi-squared tests. RESULTS: Currently, we have assessed 83 primary tumors for COX-2. Patient characteristics and incidence of CTCs and DTCs are shown in Table 1. TRN status was present in 29% (32/109), and COX-2 expression in 29% (24/83) of tumors. There was no statistically significant correlation between COX-2 and tumor size, histological type, lymph node metastases, LVI and CTC status. Significant correlations were found between COX-2 and TRN status (p =0.001, OR =5.79), tumor grade (p <0.001, OR =6.53), Ki-67 (p=0.01, OR=6.43) and presence of DTCs in bone marrow (p=0.001, OR=11.25). CONCLUSIONS: Triple receptor-negative breast tumors often express COX-2. Identification of TRN patients expressing COX-2 opens a potential avenue of treatment with COX-2 inhibitors. This is important since targeted therapy options are currently limited in TRN patients.

T1	35%(29/83)
T2	43%(36/83)
T3	11%(9/83)
T4	11%(9/83)
N(+)	50%(40/80)
COX-2	29%(24/83)
DTCs	24%(13/55)
CTCs	38% (28/73)

P36

Breast cancer risk following contralateral prophylactic mastectomy in high-risk women with a personal history of breast cancer

J.C. Boughey,[1]* T.A. Sellers,[2] S.K. McDonnell,[3] D.J. Schaid,[3] M.H. Frost,[3] A.C. Degnim,[1] C.S. Grant,[1] J.H. Donohue,[1] R.B. Jenkins,[3] L.C. Hartmann.[3] *1. Surgery, Mayo Clinic, Rochester, MN; 2. H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; 3. Mayo Clinic, Rochester, MN.*

BACKGROUND. Women with a personal history of breast cancer are at increased risk of a second primary breast cancer, especially if they have a family history or are carriers of a deleterious mutation in BRCA1 or BRCA2. The aim of this study was to estimate the potential effect of contralateral prophylactic mastectomy (CPM) in reducing risk of second primary breast cancer. METHODS. This was a retrospective analysis of two cohorts of breast cancer patients who underwent therapeutic mastectomy at the Mayo Clinic prior to 1993. The study group consisted of 488 women with stage I or II breast cancer and a family history of breast cancer who underwent a therapeutic mastectomy and a CPM. A comparison cohort of 511 unilateral breast cancer patients who underwent therapeutic mastectomy only (TMO) was matched on age at surgery, stage of disease, and year of surgery. RESULTS. The prevalence of a positive family history in the TMO cohort was 36%. Two hundred twenty women (45%) had prophylactic subcutaneous mastectomy and 268 (55%) a prophylactic total mastectomy. Through more than 9,000 person-years of follow-up (median 10.3 years), three second primary breast cancers (0.6%) were identified in the CPM cohort and 34 (6.7%) in the TMO cohort. This represented a 90% decreased risk of contralateral breast cancer (Hazard Ratio = 0.90; 95% CI: 0.03 – 0.30). Adjustment for age at diagnosis, year of surgery, stage and number of positive nodes had no effect on this estimate. Additionally adjustment for use of tamoxifen, chemotherapy, or prior history of oophorectomy did not change the results. A total of 21 patients (4%) in the CPM cohort had a known deleterious mutation in BRCA1 or BRCA2; one (5%) developed a second primary breast cancer. CONCLUSIONS. CPM for breast cancer patients with a positive family history reduces the risk of development of a second primary breast cancer by 90%.

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Radiofrequency Ablation of Breast Cancer Lumpectomy Cavities: Update with In Vivo Tissue-Based Validation of a Technique Intended to Increase Negative Margins after Breast Conservation Surgery

J.E. Coad,[1]* S. Orru,[2] M. Spinelli,[3] V.S. Klimberg,[4] M. Rais.[2] *1. Department of Pathology, West Virginia University, Morgantown, WV; 2. Azienda Sanitaria Locale, Cagliari, Italy; 3. Salvin Corona di Gardagnate, Milan, Italy; 4. University of Arkansas for Medical Sciences, Little Rock, AR.*

Breast conservation surgery is increasing in women with breast cancer. Up to 49% of these women may require additional surgery due to close or positive lumpectomy margins. This results in a significant additional burden for the patient. This in vivo study assesses the feasibility of using intraoperative radiofrequency ablation (RFA) to treat the lumpectomy cavity walls and in situ extend the final negative margins. METHODS: First, an in vitro study was performed to establish the performance characteristics of a RFA device in 12 mock lumpectomy cavities in fresh human breast or panniculus. These cavities were RFA-treated for 18 minutes with thermocouples recording the thermal history. Second, an in vivo feasibility study was performed in 10 breast cancer patients with clinically less than 2 cm tumors. The patients underwent lumpectomy, then in vivo 15 minute RFA cavity treatment, and subsequent quadrantectomy of the treated region. The devitalized tissue radii around the cavity were measured using triphenyltetrazolium chloride (TTC) viability staining. RESULTS: In vitro temperatures in excess of 55C for 5 minutes were obtained 3mm from the radiofrequency probe and exceeded 45C at the treatment region edge. The in vitro and in vivo anterior/posterior treatment zone heights were 3.9 ± 0.5 cm and 4.4 ± 1.3 cm, respectively. The in vitro and in vivo distance between the anterior ablation zone edge and adjacent skin dermis measured 1.4 ± 1.1 cm and 0.9 ± 0.6 cm, respectively. The ablation zone edge focally extended to the dermal junction in one in vivo case. The three-dimensional devitalized tissue radii are presented in the table. CONCLUSIONS: This pilot data supports the feasibility of adjuvant radiofrequency lumpectomy cavity treatment to in situ extend the mean final tissue margins by approximately 1 cm. While further evaluation of this technique's long-term efficacy is necessary, the extended margins have the potential to reduce the number of patients requiring additional surgery.

Minimum Mean TTC-Negative Radii Surrounding the RFA-Treated Lumpectomy Cavity.

	In Vitro (18mins)	In Vivo(15 mins)
Superior Wall	1.3 ± 0.3 cm	0.9 ± 0.5 cm
Superior / Posterior Wall	1.3 ± 0.3 cm	1.3 ± 0.5 cm
Inferior Wall	1.5 ± 0.3 cm	1.1 ± 0.5 cm
Inferior / Posterior Wall	1.5 ± 0.2 cm	1.2 ± 0.6 cm
Posterior Wall	1.3 ± 0.5 cm	1.1 ± 0.4 cm
Medial Wall	1.5 ± 0.5 cm	0.7 ± 0.5 cm
Lateral Wall	1.4 ± 0.3 cm	0.8 ± 0.3 cm

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Cosmesis and radiation toxicity following balloon catheter brachytherapy in early breast cancer: Preliminary 5-year results

E. Schochet,[1]* M.A. Gittleman,[2] S. Eid,[1] J. Matulay,[3] C. Bryk.[2] *1. Department of Surgery, Lehigh Valley Hospital, Allentown, PA; 2. Breast Care Specialists, Allentown, PA; 3. Muhlenberg University, Allentown, PA.*

INTRODUCTION: Balloon catheter brachytherapy (BCB) has been suggested as a suitable alternative to whole breast radiation therapy (WBRT) with similar recurrence, cosmetic, and patient satisfaction rates. While initial data has been encouraging, mature data is lacking. We report on a single-surgeon experience over the last five years. METHODS: 217 patients with DCIS and/or invasive T1-T2 breast cancer underwent lumpectomy with nodal sampling and MammoSite catheter (MC) insertion followed by BCB twice daily for 5 days. Cosmesis (Harvard scale) and toxicity (RTOG criteria) was recorded at usual intervals. RESULTS: 208 of 217 (96%) women initially implanted with the MC completed treatment. Three catheters were withdrawn due to inadequate skin spacing and cavity non-conformance, and 6 were used for boost therapy only. The subjects were 42-90 years old (mean 67.5), and had tumor sizes from 0.1 - 2.5 cm (mean 1.00); 64 women had DCIS only, whereas 132 were stage I and 11 were stage II. 37 women underwent MC insertion at the time of resection; 14 were at initial lumpectomy, and 23 at re-excision. The remaining (n=171) women underwent delayed implantation with ultrasound guidance in an office setting (n=65), or operating suite (n=106). With a mean follow-up of 33.6 months (range 4-69), cosmesis was good to excellent in 94% and poor in 1.4%. Cosmesis results over time may be seen in Table 1. Acute skin changes correlated with inferior cosmesis in the first year, while subcutaneous tissue changes predominate in later follow-up and correlate strongly with cosmesis (p=.001). There has been one contralateral breast recurrence and one ipsilateral elsewhere recurrence of DCIS. There have been no ipsilateral invasive failures. 11 patients have expired, all of whom were NED at a mean of 25.9 months from treatment. CONCLUSIONS: BCB is a well-tolerated technically feasible alternative to WBRT in early breast cancer patients. While early acute skin toxicities and late subcutaneous tissue changes remain a therapeutic challenge, good to excellent cosmesis rates are found in the 90 to 100% range at all time points.

Cosmesis Results

	1 Month	6 Month	1 Year	2 Years	3 Years	4 Years	5 Years	At Last Visit
Patients (n)	208	197	170	134	77	49	19	207
% Good to Excellent	93.6	95.1	94.1	94.8	94.6	97	100	96.9
% Poor	6.4	4.9	5.8	5.2	5.4	3	0	3.1

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Sentinel lymph node biopsy in stage I or II breast cancer patients results in significantly but not clinically relevantly better arm functioning than axillary lymph node dissection: a longitudinal prospective study J.J. Kootstra,[1]* J.E. Hoekstra-Weebers,[2] J.S. Rietman,[3] J. De Vries,[1] P.C. Baas,[4] J.H. Geertzen,[1] H.J. Hoekstra.[1] *1. Department of Surgical Oncology, University Medical Center Groningen, Groningen, Netherlands; 2. Wenckebach Institute, University Medical Center Groningen; Comprehensive Cancer Centre North Netherlands, Groningen, Netherlands; 3. Roessingh Research and Development, Enschede, Netherlands; 4. Department of Surgery, Martini Hospital, Groningen, Netherlands.*

Introduction Long-term post-operative arm functioning following Sentinel Lymph Node Biopsy (SLNB) may surpass that following Axillary Lymph Node Dissection (ALND). This study compares differences in arm functioning between ALND and SLNB in patients with stage I/II breast cancer. Methods Of the 204 patients median 54 (31-84) years who entered the study, 178 (87%) were physically examined at all measurement points: ALND 123 patients (69 %) and SLNB 55 patients (31 %). Examination was performed one day before surgery (T0) and after six (T1), 26 (T2), 52 (T3) and 104 (T4) weeks. Physical differences between affected and unaffected arm were calculated in 8 parameters. General Linear Models were computed to examine time and group effects for the entire study period (A=T0-T4) and for follow-up after surgery (B=T1-T4). Results Differences between arms in anteflexion, abduction, abduction/exorotation, abduction strength and flexion strength changed significantly over time (periods A/B: p=.05 -<.001). Differences increased between T0-T1 and decreased to an above T0 level at T4, except for flexion strength which was comparable to T0. Differences in grip strength between arms increased during period A (p=.03) but did not change during period B. ALND patients' differences between arms in anteflexion, abduction, abduction/exorotation and volume were statistically significantly greater (p=.05-<.001) than in SLNB patients in periods A and B. The two groups changed significantly differently over time in anteflexion, abduction, abduction/exorotation, abduction strength, flexion strength and arm volume during period A, and in anteflexion, abduction strength and flexion strength during period B. No significant effects were found for exorotation. Effect sizes varied between 0.136 and 0.014. Conclusion An initial decline in range of motion and strength is followed by recovery although not to pre-surgery levels. SLNB results in better outcome than ALND in range of motion and arm volume but not in strength. However, clinical relevance of these results is negligible.

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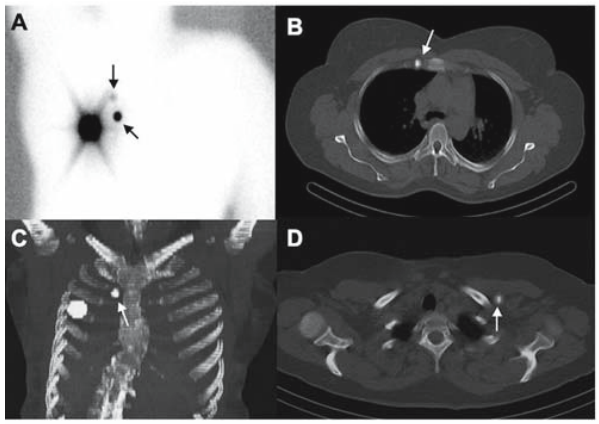
The Additional Value of SPECT/CT in Lymphatic Mapping in Breast Cancer Patients I.M. Van der Ploeg,* R.A. Valdés Olmos, O.E. Nieweg, E.J. Rutgers, B.B. Kroon. *The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.*

Introduction: Occasionally, conventional lymphoscintigraphy does not allow precise localization of the sentinel node. The recently introduced single photon emission computed tomography camera with integrated CT (SPECT/CT) fuses tomographic lymphoscintigrams with anatomical data of CT. The purpose of this study was to explore the additional value of SPECT/CT in lymphatic mapping in patients with breast cancer. Methods: Sixty-eight women with 72 breast cancers were studied. The indications for performing additional SPECT/CT were conventional lymphoscintigrams showing an unusual lymphatic drainage pattern (52 patients), conventional images that were difficult to interpret (8 patients) or non-visualization (8 patients). Results: SPECT/CT was performed immediately following conventional imaging and did not require an additional injection of the radiopharmaceutical. Conventional lymphoscintigraphy demonstrated 144 sentinel nodes in 60 of the 68 patients. SPECT/CT showed these same nodes plus 12 additional sentinel nodes in 10 (15%) of the patients. Eleven of these could be harvested and 4 were tumor-positive in 3 patients. SPECT/CT showed lymphatic drainage in all 8 patients with non-visualization on delayed conventional images. Eventually, SPECT/CT led to upstaging and a change in management in 4% of patients. In all patients, SPECT/CT established the precise anatomical location of sentinel nodes (figure). Sentinel nodes were clearly outlined when the injection site was nearby. SPECT/CT was of particular importance in determining the specific intercostal space of internal mammary sentinel nodes or establishing a location behind a rib. Such nodes were pursued. Invariably, surgeons stated that SPECT/CT improved their notion of the location of sentinel nodes and helped to better plan the operation. Conclusion: SPECT/CT detects additional sentinel nodes and shows the exact anatomical location of sentinel nodes in patients with unusual drainage or inconclusive conventional images. SPECT/CT can visualize drainage in patients whose conventional images do not reveal a sentinel node. Therefore, SPECT/CT facilitates surgical exploration in difficult cases and improves staging.



Planar lymphoscintigram of a woman with right breast cancer (A) depicts one internal mammary chain sentinel node (ascending arrow) with a second-echelon node (descending arrow). Axial fused SPECT-CT (B) and 3D SPECT/CT (C) enable tracing of the sentinel node (arrow), underneath the second rib. In another woman with left breast cancer, axial SPECT/CT fused image (D) visualizes an interpectoral sentinel node (arrow).

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The View of Medical Doctors on Breast Conservation Therapy versus Mastectomy Based Upon Years of Medical Education and Training B. Adams,* M. Amendola, A. Grover, H. Vu. *Surgical Oncology, Medical College of Virginia, Richmond, VA.*

Introduction: Objective studies have shown equivalent overall survival for breast conservation therapy (BCT) and total mastectomy (TM) in early breast cancer. The extent of personal and professional bias in supporting these treatment options has not been well defined. We hypothesize that bias for TM becomes more prevalent with increasing medical education and clinical experience. Methods: An IRB approved, web-based survey was sent to medical students, residents, and attendings over two weeks at a major US academic medical center. Respondents were asked about their gender, age, level of medical education and experience with breast cancer in friends, family members, or themselves. Respondents were then asked to choose between BCT and TM for the treatment of early breast cancer sequentially for a patient, friend, family member, and themselves. Results: The response rate was 28.4% (399 of 1408 eligible participants). BCT was found to be the preferred recommendation to patient, friend, family, and self for all education levels. First year students were most likely to advocate for TM overall, followed by residents and attendings (both $p<0.001$). In contrast, the lowest percentage of TM recommendations were made by second year students compared to advanced clinical levels ($p<0.001$). Across all experience levels, respondents were more likely to want TM for themselves than others. No difference in support for TM between men and women was found, however, women were more likely to choose TM for themselves (32.9%) versus patients (21.7%), friends (20.5%), and family (22.9%)($p=0.012$). A similar trend approached significance in men ($p=0.051$). Personal exposure to breast cancer did not impact recommendations. Conclusion: Among all education levels, BCT was the recommendation of choice for early breast cancer. However, an increase in TM recommendations was seen with increasing clinical experience starting in the second year of medical school. Surveyed women were also significantly more likely to want TM for themselves than others.

% Mastectomy Recommendations

	Patient	Friend	Family	Self	Overall
M1, n=88(22.1%)	37.2%	35.3%	36.9%	45.1%	38.6%
M2, n=65(16.3%)	1.5%	1.5%	3.1%	9.2%	3.9%
M3, n=70(17.5%)	10.3%	11.6%	17.4%	24.6%	16.0%
Residents, n=86(21.6%)	16.7%	19.1%	20.2%	30.6%	21.6%
Attendings, n=90(22.6%)	20.0%	16.7%	19.0%	30.0%	21.4%
All Education Levels	18.3%	17.9%	20.2%	28.9%	

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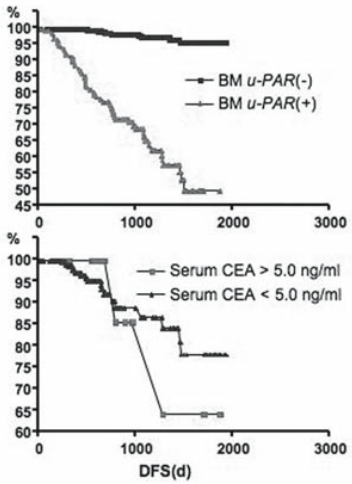
Clinical significance of u-PAR gene expression in peripheral blood and bone marrow in breast cancer cases K. Mimori,* T. Yokobori, M. Iwatsuki, K. Sakashita, Y. Takatsuno, F. Tanaka, Y. Kamohara, H. Inoue, M. Mori. *Medical Institute of Bioregulation, Kyushu University, Beppu, Oita, Japan.*

Introduction To predict the cancer recurrence, the evaluation of isolated tumor cells (ITC) in the peripheral blood (PB) or bone marrow (BM) by using epithelial cell markers such as CEA or cytokeratins (CK) would be useful. On the other hand, the significance of the expression of cancer related genes such as urokinase type plasminogen activator receptor (*u-PAR*) in PB or BM has not been clarified. **Patients and Methods** 1) We examined ITC in PB and BM from 744 cases of breast cancer (and 29 non-malignant patients as a negative control) by the quantitative real-time RT-PCR with *CEA*, *CK-19*, and *CK-7*. The ITC positive was determined when each one of the three genes was expressed. 2) The expressions of *u-PAR* in PB and BM were examined by real time RT-PCR. 3) We combined data of *u-PAR* and *CK* in comparison with each gene. 4) Serum CEA and CA15-3 levels in 298 of 744 cases were measured to compare with the *u-PAR* or *CK* status. **Results** 1) The positive result was recognized in 262 (35.4%) cases in PB, and these showed poorer disease free survival than 482 negative cases ($p<0.05$). 2) The 169 cases of *u-PAR* (+) BM showed significantly poorer disease free survival and overall survival than 575 cases of *u-PAR* (-) BM ($p<0001$ and $p <0.0001$, respectively). In PB, a significant difference was also observed between 309 cases of *u-PAR* (+) and 435 cases of *u-PAR* (-) ($p<0.0001$). 3) As for the combination of *u-PAR* and *CK* in BM, *u-PAR (+)/CK(+)* showed the highest recurrence rate, however, *u-PAR* status alone was adequate to predict recurrence in comparison with the combined data. 4) The hazard ratio for prediction of recurrence are significantly higher in *u-PAR* ($p<0.0001$; HR 0.0519) than serum CEA or CA15-3 level (not significant). **Conclusion** We found that the significance of *u-PAR* was much greater than the ITC alone. This means that the tumor-host reactions (one of those parameters may be the *u-PAR*) would be very important to predict the cancer recurrence rather than the existence of cancer cells in the circulating system, and would be much more reliable than the established serum tumor markers preoperatively.



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Use of PET/CT as the initial staging tool in clinical Stage 3 Breast Cancer W.C. Dooley,* C.L. Troup, J. Parker. *Breast Institute, University of Oklahoma, Oklahoma City, OK.*

Introduction: PET/CT has become popular in staging cancers at significant risk for metastasis at presentation. In some communities PET/CT has begun to replace Ct of chest and abdomen and Bone Scan as the initial screening evaluation for clinically occult metastasis in breast cancer. Methods: This is a retrospective review of PET/CT in a single surgeons practice over a 15 month period (9/2005-12/2006). PET/CT was used exclusively for the initial staging of clinical stage 3 breast cancer during that interval. On review of electronic charts, 76 clinical stage 3 patients were identified as presenting during the interval and ranged in age from 21-96 years old. All subsequent imaging and follow-up was reviewed for a period > 6 months to identify confirm systemic metastasis sites or refute them with additional testing and/or imaging. Results: In this patient series, 42% had PET/CT findings consistent with metastasis but only 39% could be confirmed by additional testing. In subsequent follow-up, 27% continue to have evidence of disease persisting in spite of systemic therapies. PET/CT findings could be confirmed by traditional IV contrasted CT in 33% of cases. Bone scan confirmed PET/CT findings in 9% but refuted them in 3%. MRI scans confirmed PET/CT findings in 15%. Sensitivity was 100% in this series with early follow-up but specificity was 95%. The PPV was 93% and the NPV 100%. Conclusions: PET/CT is a valuable tool in pre-treatment screening of stage 3 breast cancer. Prospective studies should be organized to determine the most cost effective method to screen for systemic metastasis in the high risk group of clinical stage 3 breast cancer patients.

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Focused parathyroidectomy for primary hyperparathyroidism: Not a good choice for everyone Z. Shafaee,* S. Kaplan, L. Ahmed, E. Kaplan. *surgical oncology, the university of Chicago hospitals, Chicago, IL.*

Goals: Evaluation of accuracy of preoperative localizing studies, to correctly identify the pathologic glands in cases of primary hyperparathyroidism, and feasibility of focused approach parathyroidectomy. Also assessment of reliability of intraoperative PTH measurement in predicting cure. Methods: We retrospectively reviewed our prospectively collected data base of 100 consecutive patients who underwent parathyroidectomy for primary hyperparathyroidism. All patients underwent four quadrant neck explorations, by a single endocrine surgeon (EK). All patients had intraoperative intact PTH measurement at different time points before and after excision of the gland(s). Settings: All operations were done in a University Hospital. Results: In our series of 100 consequentive patients the success rate was 96%.79% of cases were single adenoma, and 21% were multiple adenomas. The average weight of the gland for single adenoma cases was 1031 mg, and for multiglandular disease were 394 mg. The sensitivity of Sestamibi scan in single adenoma cases was 65% and positive predictive value was 89%. Sensitivity and PPV of Sestamibi scan for multiple adenoma cases were 13% and 40% accordingly. For UltraSound the sensitivity and PPV were 62% and 85% in single adenomas v.s.18% and 60% in multiple adenomas. For both tests the sensitivity and PPV were directly related to weight of the gland. US and Sestamibi concurred in 50% of single adenoma cases vs. 33% in multiple adenoma cases . All patients who were cured had more than 50% drop in iPTH level intraoperatively and PTH level returned to normal range. One patient with single adenoma and 3 patients with multiple adenomas were not cured. 3/4 of patients who were not cured had more than 50% drop in iPTH level intraoperatively. Conclusion: focused approach based on US and sestamibi scan is feasible in cases which US and Sestamibi concur. That is a small percentage of cases with primary hyperparathyroidism. Intra-OP PTH drop >50% is not a reliable predictor of cure.

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An outcomes analysis of laparoscopic versus open adrenalectomy
P.C. Tang,* S.A. Roman, J.A. Sosa, K. Cheung, R. Udelsman. *Surgery, Yale University, New Haven, CT.*

Introduction: Laparoscopic adrenalectomy (LA) has become the standard approach for excision of benign adrenal tumors. The aim of this study was to analyze the outcomes and changing practice patterns of LA versus open adrenalectomy (OA) by adrenal lesion type. Methods: In this retrospective review of an institutional series, 209 consecutive patients who underwent adrenalectomy were identified (LA n=131, OA n=78) in a university center from 1985 to 2006. Patient demographics, perioperative outcomes, and tumor characteristics were recorded. Results: LA currently represents 86% of all adrenalectomies. No differences in gender, age, or comorbidity were noted between patients undergoing LA or OA. LA achieves a decreased hospital length of stay (LOS) (2.8 vs. 9.1 days, p<0.0001), surgical intensive care (SICU) stay (0.8 vs. 1.7 days, p<0.0001), complications (0.21 vs. 0.44 per admission, p=0.018), and estimated blood loss (EBL) (110 vs. 814 ml, p<0.001). LA resulted in decreased hospital LOS and EBL for all four tumor types (Table). SICU stays were shorter for LA in pheochromocytomas (n=34) (1.3 vs. 2.5 days, p<0.05), and cortisol-secreting adenomas (n=22) (0.2 vs. 2.7 days, p<0.05) but not aldosteronomas (n=42) (0.3 days for both) or nonfunctional adenomas (n=22) (0.5 vs. 1.1 days). Comparing LA outcomes by adrenal tumor type, LA for pheochromocytomas resulted in longer SICU stay (1.3 days) than nonfunctioning adenomas (0.5 days, p<0.05), aldosteronomas (0.3, p<0.05), and cortisol-secreting adenomas (0.2 days, p<0.05); longer hospital LOS when compared to aldosteronomas (2.7 vs. 2.1 days, p<0.05), and higher EBL (130ml) compared to aldosteronomas (53 ml, p<0.05) and cortisol-secreting tumors (67 ml, p<0.05) (Table). Conclusions: This series of 209 consecutive patients supports the conclusion that LA is the procedure of choice for the vast majority of benign adrenal tumors. LA is associated with improvements in LOS, SICU days, complications and EBL. Subgroup analyses confirm the advantages of LA for non functional adrenal adenomas, pheochromocytomas, and cortisol-secreting adenomas.

Table 1. Outcomes based on tumor type

Tumor type	Pheochromocytoma		Aldosteronoma		Cortisol-secreting adenoma		Nonfunctional adenoma	
	LA (n=34)	OA (n=29)	LA (n=36)	OA (n=6)	LA (n=22)	OA (n=9)	LA (n=22)	OA (n=14)
Hospital stay (days)	2.7*	11.2	2.1*	5.2	2.6*	14.9	2.3*	7.0
SICU stay (days)	1.3*	2.5	0.3	0.3	0.2*	2.7	0.5	1.1
EBL (ml)	130*	1293	53*	308	67*	728	75*	714
Average number of complications	0.2*	0.6	0.1	0.2	0.2	0.3	0.1	0.4
Tumor size (cm)	4.0*	6.3	1.6	1.6	3.5*	8.9	4.2	7.1

*p<0.05 Laparoscopic vs Open

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Central Neck Dissection in Node Negative Papillary Thyroid Cancer: Is it Overkill or the Optimal Operation? D. Abraham,[2] D. Repplinger,[1] Y. Zhang,[1] H. Chen,[1] R.S. Sippel.[1]* *1. Surgery, University of Wisconsin, Madison, WI; 2. Christian Medical College, Tamil, Nadu, India.*

Introduction: Recent guidelines state that a central neck lymph node dissection should be performed as part of the initial operation for patients with clinically node negative papillary thyroid cancer (PTC). While lymph node recurrences are common in PTC, the risk of central neck node recurrence after thyroidectomy alone, is not well established. The objective of this study was to look at central neck node recurrence following total thyroidectomy alone for clinically node negative PTC. Methods: Retrospective review of all patients with clinically node negative PTC treated in a single tertiary care teaching hospital over a thirteen year period (1994-2006). Patient characteristics, complications, lymph node recurrences and survival were analyzed. Results: Two hundred and forty nine patients (57 male and 142 female) underwent thyroidectomy (hemithyroidectomy n=41, total thyroidectomy n=208) for clinically node negative PTC. The median age of the patients was 45.7 (range 12.4-87.3). The mean nodule size was 1.8 cm (range 0.01-9 cm). The mean follow up time was 36 months (range= 0- 129). Overall, neck lymph node recurrence occurred in 6.5% (16/249) of patients. Central neck lymph node recurrence was seen in only 2.8% (n=7) of patients. Patient age, gender, and nodule size were not associated with a higher risk of recurrence. Mortality was 1.2% (n=3) and complications occurred in 2% of patients. Permanent hypoparathyroidism (requiring calcium supplements greater than 6 months) occurred in 1.2% (n=3) and recurrent laryngeal nerve injury occurred in 0.8% (n=2). Conclusions: The risk of central neck lymph node recurrence was only 2.8% in patients with clinically node negative PTC. Given the low rate of central neck node recurrences in these patients, after total thyroidectomy alone, the risk benefit ratio of a routine central neck dissection needs to be carefully evaluated.

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Role of surgeon-performed ultrasound in predicting malignancy in patients with indeterminate thyroid nodules W. Mendez,* J.I. Lew, S.E. Rodgers, R. Montano, W. Sumner, C.C. Solorzano. *Surgery, University of Miami, Miami, FL.*

Introduction: Certain ultrasound features can predict malignancy in patients with thyroid nodules. The purpose of this study was to determine the value of office based surgeon-performed ultrasound (SUS) in predicting thyroid malignancy in patients with indeterminate fine needle aspiration (FNA) cytology. Methods: From 2002 to 2007, 477 consecutive patients underwent FNA of dominant thyroid nodules. Of these patients, 180/477 (38%) were judged to have indeterminate cytology: follicular neoplasm (FN, n=108), Hurthle cell neoplasm (HN, n=29) and "suspicious papillary thyroid cancer" (SPTC, n=43). SUS-characteristics for thyroid nodules were recorded prior to thyroidectomy and entered into a prospective database. Variables analyzed included patient's age and sex, nodule size, shape, echogenicity, consistency (solid/cystic), borders, multiplicity/multi-centricity and presence of microcalcifications. Features of thyroid nodules were compared to final pathology. Univariate and multivariate analyses were performed. The accuracy of individual SUS features as well as the presence of 2 or more adverse features in predicting malignancy was also examined. Results: There were 144 females and 36 males. The mean age was 52 years (17-87). The mean tumor size was 2.7cm (0.65-6.6). Overall, final pathology revealed cancer in 91/180 (50%) patients. Malignancy was present in 40/108 (37%) FN, 11/29 (38%) HN, and 40/43 (93%) SPTC. On univariate analysis, the presence of microcalcifications correlated highly with malignancy with a specificity, positive predictive value (PPV), and accuracy of 81%, 75%, and 70%, respectively. On multivariate analysis, solid nodules, shape (taller>wider), hypoechogenicity and presence of microcalcifications were significantly associated with malignancy (p<0.01). The presence of 2 or more adverse SUS features had a specificity, PPV and accuracy of 83%, 79% and 72%, respectively, in predicting malignancy. Conclusion: Adverse thyroid nodule features seen on SUS may provide additional information in predicting malignancy and help determine the initial extent of thyroidectomy in patients with indeterminate FNA cytology.

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Parathyroidectomy Reduces Fracture Risk in Patients with Primary Hyperparathyroidism Regardless of Bone Mineral Density
P.I. Haigh,* L. VanderWalde, I. Liu. *Surgery, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA.*

Introduction: Bone mineral density is one parameter used to decide whether patients with primary hyperparathyroidism (PHPT) should undergo parathyroidectomy. However, the influence of bone mineral density and parathyroidectomy on subsequent fracture risk is unclear. Methods: Retrospective cohort study of patients with PHPT using administrative discharge abstract data. DEXA scan T-scores at the femur were collected by chart review. 10-year fracture free survival (FFS) was the main outcome measured. Results: There were 533 patients identified. The majority of patients were ≥50 years old (89%) and female (87%). Seventeen percent of patients were black. Mean initial calcium, parathormone, and creatinine levels were 11.1 mg/dL, 116 pg/mL, and 0.9mg/dL, respectively. Parathyroidectomy was performed in 159 (30%) patients, and 374 (70%) were observed. The 10-year FFS after PHPT diagnosis was 94% in patients treated with parathyroidectomy compared to 81% in those observed (P=0.006). Compared to observation, parathyroidectomy increased the 10-year FFS by 9.1% (P=0.99), 12% (P=0.92), and 12% (P=0.02) in patients with normal bones (T-score ≥-1.0), osteopenia (T-score ≤-1.0, ≥-2.5), and osteoporosis (T-score <-2.5), respectively. On multivariate analysis, parathyroidectomy was independently

associated with decreased fracture risk (HR=0.41; 95% CI 0.18, 0.93), whereas non-black race (HR=2.94; 95% CI 1.04, 8.30) and T-score <-2.5 (HR=2.29; 95% CI 1.08, 4.88) remained independently associated with increased fracture risk. Age ≥50 (HR=1.44; 95% CI 0.51, 4.03), initial parathormone level (HR=0.99; 95% CI 0.99, 1.01) and calcium level (HR=1.19; 95% CI 0.67, 2.11) were not independently associated with fracture risk after adjusting for all other variables. Conclusions: Parathyroidectomy decreases the risk of fracture in patients with normal bone mineral density, osteopenia, and osteoporosis. The largest impact from parathyroidectomy is in patients with osteoporosis.

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The Influence of Surgical Approach on Quality of Life After Parathyroid Surgery J.T. Adler,* R.S. Sippel, H. Chen. *Surgery, University of Wisconsin, Madison, WI.*

BACKGROUND: It is well established that quality of life improves after parathyroidectomy. Less well understood is the impact of surgical approach on quality of life during recovery. The potential advantages of a minimally invasive approach include improved cosmesis, reduced postoperative pain, and a shorter length of stay. This study was undertaken to determine if surgical approach plays a role in quality of life improvements after surgery for hyperparathyroidism (HPT). METHODS: 146 consecutive patients who underwent parathyroidectomy for HPT were administered the SF-36 Health Survey one week before, one week after, and one year after surgery. Clinical data were gathered to correlate with quality of life measurements. RESULTS: 96 patients had a minimally invasive parathyroidectomy, while 48 patients had bilateral explorations. All patients were normocalcemic >6 months after surgery. Length of stay was significantly shorter in those undergoing a minimally invasive operation (0.2±0.04 vs. 0.9±0.04 d, $P < 0.001$), and the complication rate was not statistically different (3.1% vs. 6.3%, $P = 0.40$). In the 10 SF-36 scales, the patients improved significantly in 5 scales after one week and all 10 scales after one year. When separated by surgical approach, the minimally invasive group improved significantly in 4 scales one week after operation, while those with a bilateral exploration improved in 2. After one year, the minimally invasive group had statistically improved in 8 categories, while the bilateral exploration group did so in only 4 ($P < 0.05$ for all). CONCLUSIONS: Quality of life improved after surgery for HPT, irrespective of surgical approach. This was observed even one week after surgery. While there was an equal cure rate in both groups, the minimally invasive approach was associated with greater improvements in quality of life and a shorter length of stay. Importantly, the minimally invasive group improved in twice as many categories at both one week and one year. With better surgical outcomes and improvements in quality of life, these data provide additional evidence that minimally invasive parathyroidectomy is the operation of choice for patients with HPT.

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Functional Voice Implications of Sternothyroid Muscle Division During Thyroidectomy L.R. Henry,[1]* A. Shaha,[2] N. Solomon,[3] R. Howard,[3] J. Gurevich-Uvena,[3] L. Horst,[3] R. Orlikoff,[4] S. Libutti,[5] A. Stojadinovic.[3] *1. Department of Surgery, National Naval Medical Center, Bethesda, MD; 2. Memorial Sloan Kettering Cancer Center, New York, NY; 3. Walter Reed Army Medical Center, Washington, DC; 4. Seton Hall University, South Orange, NJ; 5. National Cancer Institute, Bethesda, MD.*

Introduction: Voice dysfunction may occur after thyroidectomy in the absence of laryngeal nerve injury. Strap muscle division has been implicated as one potential etiology, though the clinical implications of muscle division are undefined. Methods: Prospectively recorded functional voice outcomes data after thyroidectomy were utilized from two tertiary, high-volume referral institutions. Patient reported symptoms at one week and three months post op were documented. Laryngoscopic, acoustic, and aerodynamic parameters were recorded pre-, 1-2 weeks and three months post-operatively. Patients with and without sternothyroid muscle division during operation were compared for incidence of reported voice changes and alterations in acoustic and aerodynamic measurements from preoperative values. Patients with laryngeal nerve injury, sternohyoid division, arytenoid subluxation or no follow-up evaluation at 1-2 weeks post op were excluded from the analysis. Differences between the study groups and outcomes were compared using the 2-sided t-test. Results: There were 84 patients studied, 45 of whom had sternothryoid muscle division. The groups were similar with regard to age, gender, extent of thyroidectomy (lobe vs. total), specimen size, as well as laryngeal nerve identification rates. There was a significant predilection for or against sternothyroid division according to medical center. No significant difference in reported voice changes was observed between groups post-op at 1-2 weeks (15/45 with, 12/39 without division, p=.82) or three months (7/45 with, 2/39 without division, p=.10). Changes from baseline in acoustic and aerodynamic parameters did not differ significantly between groups at the post-operative study time points. Conclusions: Sternothyoid muscle division is an important technical maneuver during thyroidectomy to gain superior pedicle exposure. Division of this muscle does not appear to be associated with adverse functional voice outcome and should be utilized at surgeon discretion during thyroidectomy. The views expressed herein are those of the authors and do not reflect the policy of the U.S. Navy, U.S Army, Department of Defense, nor the U.S. Government.

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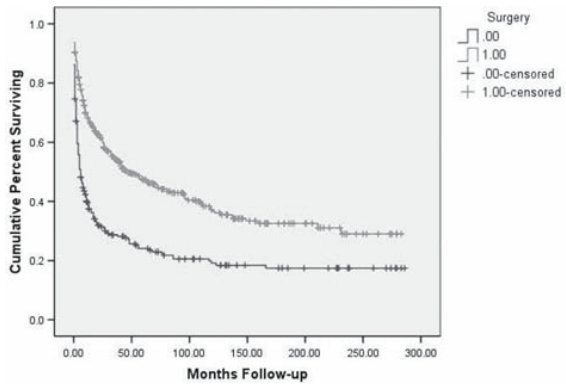
Adrenal Cortical Carcinoma: Patterns and Results of 768 Cases from the FCDS W.E. Sumner,* D. Franceschi. *Surgical Oncology, University of Miami, Miami, FL.*

Introduction: Adrenal cortical carcinoma is a relatively rare tumor whose course historically depends on size and stage at presentation. The Florida Cancer Data Registry is one of the largest single incident cancer data registries in the country, which we queried to investigate patterns of this disease. Methods: Patients with ACC from 1981 to 2004 with adrenal cortical carcinoma were identified. Descriptive statistics, treatment patterns, and survival and associated factors were calculated. Results: A total of 768 ACC patients were identified. Median age was 63 years, and tumors were distributed equally among males and females. 82% of patients were white, 6.6% African American, and 10% Hispanic. Median tumor size was 9 cm. With respect to grade, half were poorly differentiated, 21% were undifferentiated, and 15% were well and moderately differentiated respectively. ACC was treated with surgical resection in 59% of patients, chemotherapy in 18%, and radiation in 10%. Median survival was 23 months with a median follow up of 15 months. Median survival was considerably improved with surgical intervention, 47 months v. 6 months ($p < .001$) (Figure 1). Poorer survival was also significantly associated with increasing tumor size, higher grade, and SEER stage at diagnosis. Patients receiving chemotherapy or radiation fared worse, likely reflecting more advanced disease in these patients. There was no significant increase in tumor size with more recent year of diagnosis. Conclusions: Surgical resection is associated with significantly increased survival in patient's with ACC. Those with poor features such as high grade, large size, and advanced stage continue to have poor outcomes. Despite more widespread use of computed tomography, tumor size at diagnosis has not changed significantly with more recent diagnosis. Research into more efficacious adjuvant regimens may improve on surgery alone in patients with advanced disease.



Survival in ACC with and without surgical resection.

P52

The Role of Pancreatic Metastectomy: A Retrospective Analysis of the Largest Single Institutional Series S. Reddy,* B.H. Edil, J.L. Cameron, T.M. Pawlik, J.M. Herman, M.M. Gilson, R.D. Schulick, M.A. Choti, C.L. Wolfgang. *Department of Surgery, Johns Hopkins Hospital, Baltimore, MD.*

Introduction: Hepatic and pulmonary resections of metastatic lesions have been shown to improve outcome for certain cancers. The outcome of patients undergoing pancreatic metastectomy (PM) is not well characterized. The goal of this study is to report the efficacy and safety of PM. This is largest single institutional experience reported on this topic to date. Methods: We performed a retrospective analysis of a single institution's prospectively gathered pancreaticobiliary database from 1970 to 2006. We identified all patients who underwent a PM and collected demographic, clinical and pathological data. Results: During this time period 3830 patients underwent a pancreatic resection at our institution. Sixty (1.6%) had resections of pancreatic or periampullary lesions from non-pancreatic primary cancers. Eleven patients had lymphoma and were excluded from further data analysis. Thirty-one patients (63%) had pancreaticoduodenectomies, 14 (29%) had distal pancreatectomies and 4 (8%) had total pancreatectomies. Pathology distribution was as follows: 21 renal cell carcinoma (RCC), 6 gallbladder cancer, 4 lung, 4 ovarian, 4 sarcoma, 3 melanoma, 2 colon, 1 breast, 1 hepatocelluar carcinoma, 1 seminoma and 1 Langerhans Cell Histiocytosis. Post-operative morbidity was 45% without any operative mortality. Median follow-up was 31 months. The overall median survival for all cancer types was 35 months. Results of univariate and multivariate analysis are shown in the figure. We performed subset analysis of patients with RCC. Eighteen (86%) patients with RCC had metachronous lesions. The median length between initial operation and metastectomy was 9.4 years. The median survival for RCC was 4.8 years. Metachronous lesions had similar survival as synchronous lesions (Hazard ratio 1.091, p = 0.90). Conclusions: The morbidity of PM is similar to resection of primary pancreatic cancer. RCC patients have improved prognosis compared to other cancers, while melanoma has the poorest prognosis. PM has comparable long-term survival to that reported for pulmonary metastectomy of RCC. Our results demonstrate PM in select group of patients is a safe and effective therapy.

Univariate Analysis		
Variable	**Hazard Ratio**	**P value**
RCC vs. Any other	**0.10**	**< 0.05**
Male Sex	**1.97**	**0.07**
Absence of Post-operative complications	**0.47**	**0.05**
Melanoma vs. All others	**8.42**	**< 0.001**
Multivariate Analysis		
Variable	**Hazard Ratio**	**P value**
Melanoma	**13.48**	**< 0.001**
Male Sex	**2.57**	**0.02**

Note: Only statistically significant or near significant variables are shown.

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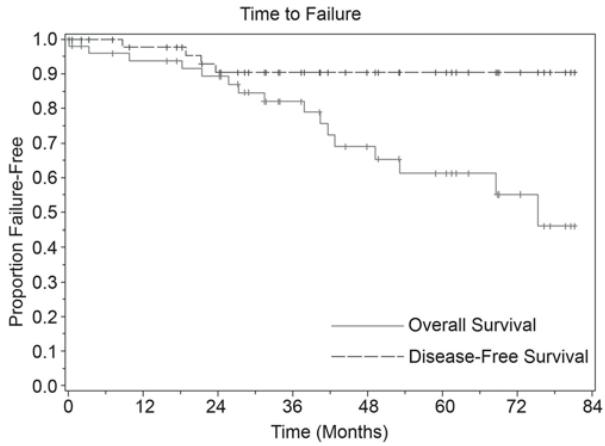
Can Colon Cancer Patients Adequately Staged as T3N0 be Cured with Surgery Alone J.W. Jakub,[1]* E.A. Levine,[2] J. Paramo,[3] S. Shivers,[1] G. Russell,[2] D.S. Reintgen.[1] *1. Lakeland Regional Cancer Center, Lakeland, FL; 2. Wake Forest University, Winston-Salem, NC; 3. Mount Sinai Medical Center Comprehensive Cancer Center, Miami, FL.*

Introduction: The role of adjuvant chemotherapy for colon cancer patients staged T3N0 is controversial. We examined whether T3N0 patients staged by an adequate lymph node harvest as well as focused pathologic evaluation of the lymph nodes would have an excellent prognosis with surgery alone. Methods: Three institutions combined their prospective databases of surgically resected colon cancer patients. All patients had T3N0 colon cancers on final pathology after undergoing lymphatic mapping and SLN biopsy with focused pathologic analysis of SLNs including IHC staining. Chemotherapy was administered at the discretion of the medical oncologist. Kaplan Meier survival curves were utilized. The log-rank test of the chi-square approximation was used to compare overall survival (OS) and recurrence free survival. To compare ages between the chemotherapy and non-chemotherapy subjects, the Wilcoxon Two-Sample Test was used. Results: 51 patients with T3N0 colon cancer were identified with a median follow-up of 53.1 months. The mean age was 67 for the entire group, 61 for those who received adjuvant chemotherapy and 69 for those who did not. The mean number of lymph nodes examined per patient was 15.6 (range 3-49, SD 9.9). The recurrence free survival for the entire group was 90%(Fig 1). However, the 5-year OS was only 61.3% with 13 patients dead in follow-up from other causes. Twelve patients received adjuvant chemotherapy. There were no recurrences or deaths in this group and a statistically significant improvement in OS(p=0.007). Of those who did not receive adjuvant chemotherapy there was an 87% recurrence free survival (p=0.22). 4 patients were staged T3N0(i+). None of these patients had documented recurrence. However, the IHC positive groups OS was statistically worse than the IHC negative group (p=0.009), with three of these patients dead from causes other than colon cancer. Conclusions: This study supports the concept that patients pathologically staged T3N0 with an adequate surgical resection and pathologic evaluation have an excellent recurrence free survival. The utility of chemotherapy in this group is unclear, and appears to play a less important role than adequate surgical staging.



P54

A Clinicogenomic Comparison of Colorectal Cancers In Young and Elderly Patients J.M. Lewis,* J.M. McLoughlin, R.M. Nair, E.M. Siegel, G.C. Bloom, S. Eschrich, T.J. Yeatman, D. Shibata. *H. Lee Moffitt Cancer Center, Division of Interdisciplinary Oncology, Tampa, FL.*

Introduction: Colorectal cancer (CRC) in young patients may represent distinct clinicopathologic and genetic subsets from CRC occurring in elderly patients. Using a comprehensive clinicogenomic database, we have sought to identify differences between CRCs occurring in young and elderly patients

without known inheritable predisposition. Methods: From 1993-2003, 174 primary CRC tissues were identified from patients consenting to a tissue collection protocol. Of these, 11 were ≤ 45 years old and 27 were ≥ 80 years old. These patients form the basis of our current analysis. RNAs were extracted from all specimens and processed for gene expression profiling. Results: Clinicopathologic features for both cohorts are listed in Table 1. Though young patients presented with more advanced stage, and were more likely to receive adjuvant therapy, the overall survival and recurrence rates were not significantly different between the two groups. Gene expression analysis revealed a dramatic difference between the two cohorts. At a false discovery rate of 0.05, the young cohort displayed 427 up-regulated and 976 down-regulated genes as compared to the elderly cohort. By gene ontology software analysis, 38 biologic pathways were identified as being significantly upregulated in tumors from the young group. The top 9 significantly upregulated pathways included those involving Cell Adhesion and/or Cell Signaling (e.g. Chemokines and adhesion p<0.0001; TGF/WNT and cytoskeletal remodeling p=0.0017; Fibronectin binding integrins p=0.0014). Conclusions: Clinicopathologic outcomes were similar, however, CRCs from young and elderly patients show dramatic differences in gene expression profiles. Although some changes can be accounted for by aging processes, there are clear alterations in a number of oncogenic pathways, particularly in those relating to cell adhesion. Our findings have implications for further elucidating novel genetic mechanisms underlying the development of colorectal cancer in young patients.

Clinicopathologic factors identified comparing young and elderly patients with colorectal cancer.

Clinical Parameter	Young (≤45)	Elderly (≥80)	p-Value
Median Follow-up (Months)	50 (11-141)	44 (2-133)	0.49
Caucasian	7/11 (64%)	27/27 (100%)	0.05
Male	8/11 (73%)	9/27 (33%)	0.04
Advanced Stage (III/IV)	8/11 (73%)	10/27 (37%)	0.03
Adjuvant Therapy	9/11 (82%)	7/26 (27%)	0.00
Recurrent Disease	4/11 (36%)	4/27 (15%)	0.14
Overall 5-year Survival	61%	50%	0.78

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The significance of peritoneal lavage cytology in colorectal cancer patients I. Lee,* Y. Lee, S. Oh, S. Chang. *The Catholic University, St. Mary's Hospital, Seoul, South Korea.*

Background: To evaluate the clinical relevance of peritoneal lavage cytology as the predictors of peritoneal metastasis and a prognostic indicator in patients with colorectal cancer. Methods: Peritoneal lavage samples of 116 patients (20 patients whose retained fluid was more than 50cc between May 2004 and December 2005 and consecutive 96 patients between January and December 2006) with colorectal adenocarcinoma were immunocytologically analyzed, including a staining of CEA, calretinin in cytology cell block. Results: The incidence of exfoliated free cancer cell was 7.8% (9 patients), and 77.8% (7 patients) of them had more than 10cc body fluid retained in the Douglas pouch. Positive cytology was 5 cases (55.6%) through Papnicolaou and Giemsa stainings and 8 cases (88.9%) through CEA and calretinin immunohistochemistry. The tumor with cytology positive was located in the right colon in 4 patients (44.4%), the transverse colon in 1 patients, rectosigmoid colon in 3 patients and 1 patient was recurrence cancer with Kurkenberg tumor. Univariate analysis of the prognostic factors revealed that peritoneal effusion with more than 10cc body fluid retained in the Douglas pouch (p=0.028), peritoneal metastasis (0.009), histology (0.001), the depth of invasion (<0.001), lymph node metastasis (0.005), distanat metastasis 0.006), Duke's classification (0.033), and age (0.014) were significantly correlated to positive cytology. In multivariate analysis, only the depth of invasion correlated significantly. Of the eight patients with positive cytology, six patients developed recurrence and 5 patients (83.3%) of them had peritoneal recurrence. The mean cancer free survival time of the patients with positive and negative cytology were 12.2±3.9 and 24.9±2.1 months, respectively (p<0.001). Conclusion: Cytology through CEA and calretinin immunohistochemisty improves the positive rate of cytology. The results of peritoneal lavage cytology were correlated to advanced cancer, especially, the depth of invasion, and useful predictor of recurrence.

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Defining Surgical Indications for Type 1 Gastric Carcinoid R. Gladdy,* V. Strong, C. Coit, P. Allen, H. Gerdes, D. Klimstra, J. Shia, M. Brennan, L. Tang. *Memorial Sloan-Kettering Cancer, New York, NY.*

Introduction:Type 1 gastric carcinoids (GC) occur in association with achlorhydria, hypergastrinemia, atrophic gastritis and exhibit low grade histopathology. The management of this disease is controversial. The aim of this study is to demonstrate whether endoscopic surveillance compared with surgical resection is warranted for Type 1 GC. Methods:Between 1985 and 2007, 65 Type 1 GC patients were identified from a prospective institutional database. Data analysis included: demographics, endoscopic assessment, pathologic evaluation, and type of surgery performed. The primary endpoints were disease-specific survival(DSS)in both groups and recurrence-free survival (RFS)in those surgically resected. DSS and RFS were calculated using the Kaplan-Meier method. Results:The median follow up was 30 months (1-176). The median age at diagnosis was 58 years (29-91), and most patients were female (83%). All patients diagnoses were confirmed by histopathology;65% had documented hypergastrinemia. Patients were managed by either surveillance endoscopy with polypectomy or gastric resection. Surgery was performed in patients with larger tumor size, increased depth of invasion, and solitary tumors (Table). There was an increasing trend toward endoscopic surveillance as 43% of patients were treated with surgical resection from 1985-92,41% from 1993-99 and 21% from 2000-07. Although the 5 year RFS in surgically resected patients was 75%, the DSS in both groups was 100%*. Concomitant adenocarcinoma was identified in 4/19 resected cases; 2/4 were detected on pre-operative biopsies. All cases with co-existing gastric adenocarcinoma had larger carcinoid tumors and more advanced carcinoid disease (2.3±0.8cm; 3/4 with carcinoid nodal disease). Conclusions:The DSS is excellent for Type 1 GC patients treated with endoscopic polypectomy or surgery. Surgical resection should be considered in patients with more advanced carcinoid disease given the increasing risk of nodal metastases and an association with an increased risk of adenocarcinoma. Annual surveillance endoscopy is appropriate for selected patients to assess the status of carcinoid disease, risk of gastric mucosal dysplasia/adenocarcinoma, and following surgical resection.

	Size (cm) (p=0.01)	Invasion beyond submucosa (p=0.02)	% Solitary (p<0.01)	Months of Endoscopic Surveillance	Survival (5 year)*
Surveillance (n=46)	0.5±0.1	0/46	9%	24.6 (1-157)	100% DSS
Resection (n=19)	1.3±0.3	3/19 (16%)	42%	3.1 (0-11)	100% DSS 75% RFS

P57

nhibitive and radiosensitizing effects of 2-methoxyestradiol on liver metastases of colon cancer in a zenograft mice model C. Xing,* Y.Y. Wu, Z.Y. Ma. *General Surgery, 2nd Hospital of Soochow University, Suzhou, China.*

Background: 2-methoxyestradiol (2-ME) is an endogenous estradiol metabolite with promise for the treatment of malignancies. The current study was designed to investigate its effects on liver metastases of colon cancer and its influences on the responses of metastatic lesions to radiotherapy. Materials and methods: The animal model with liver metastases of colon cancer was established by injecting human LS147T colon cancer cells into the spleen of the nude mice. The mice were then randomized into seven groups, the PBS(100mg.kg-1)control group, 2-ME (50 mg.kg-1)group, 2-ME (100 mg.kg-1)group, 2-ME (150 mg.kg-1)group, 2-ME(100mg.kg-1)+radiotherapy group, 2-ME(150 mg.kg-1)+radiotherapy group and PBS(100mg.kg-1)+radiotherapy group. Three weeks after model establishment, 2-ME or PBS was administered daily for 7 days. Five weeks after the establishment of animal model, 3 groups accepted radiotherapy of the liver region every other day for 10 days, with a total dose of 11.5Gy. The mice were sacrificed seven weeks later for further evaluation of tumor weight, inhibition rate, microvessel density (MVD) and apoptotic index (AI). Results :The weights of metastatic tumors of the liver were1.28±0.31g, 0.72±0.18g, 0.48±0.12g, 0.21±0.08g, 0.31±0.09g, 0.14±0.06g, 0.92±0.23g, respectively, in the seven groups. MVDs were 17.5±5.8, 9.1±2.7, 3.3±1.3, 0.85±0.6, 2.9±1.5, 0.71±0.9, 14.3±4.3, inhibition rates were 0%, 43.8%, 62.5%, 83.6%, 75.8%, 89.1%, 28.1%, and AIs were 4.56±2.71, 7.21±4.25,

17.35±4.78, 20.15±5.34, 24.75±4.36, 25.89±7.34, 6.98±3.75, respectively. Compared with the untreated controls, tumor metastases to the liver was inhibited significantly in a dose-dependent pattern ($p<0.05$). The inhibitive effect was most obvious in the 2-ME (150mg.kg-1)+radiotherapy group. Conclusions: As a potent anti-angiogenetic agent, 2-ME remarkably inhibited the liver metastases of colon cancer by its anti-angiogenetic and apoptosis inducing properties. 2-ME exhibited synergistic effects with radiotherapy, with its underlying mechanism still to be elucidated.

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RT-PCR enhances the detection of subclinical metastasis in patients with gastric and pancreatic cancer K. Kelly,* R. Gladdy, Y. Woo, K. Moore-Dalal, M. Gonen, P. Allen, Y. Fong, D. Coit. *Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction: Positive peritoneal cytology predicts poor outcome in gastric and pancreatic cancer. Conventional assessment by Papanicolaou staining may lack sensitivity as early peritoneal recurrence occurs in cytology negative patients. The purpose of this study was to define the increased yield of detection of peritoneal disease by RT-PCR over conventional cytology in gastric and pancreatic cancer. Methods: Between Feb and Aug 2007, peritoneal washings were collected from gastric and pancreatic cancer patients at the time of staging laparoscopy. Specimens obtained from three sites (RUQ, LUQ, pelvis) were analyzed by RT-PCR for a panel of markers: CEA, CK20, Survivin, and MUC2 (gastric), or CEA, CK7, MUC1, and Kras2 (pancreatic). Cancer cell lines, cytology+ washings, and washings from patients with gross peritoneal disease served as positive controls, and benign washings as negative controls. Results: For both diagnoses, all cytology+ patients were also PCR+. Within the group of 50 gastric cancer patients, 9 (18%) were cytology+ and 20 (40%) were RT-PCR+. For the 11 patients with cytology- / PCR+ disease, 8 had T3N0/1M0 disease and 3 had M1 disease (with peritoneal implants). Within the group of 42 patients with pancreatic cancer, 6 (14%) were cytology+ and 20 (48%) were PCR+. For the 14 patients with cytology-/PCR+ status, more advanced disease was observed: T2N1M0 (n=1), T3N1M0 (n=5), T4NXM0 (n=2), and M1 (n=6). Results are categorized by stage below (Table). Conclusions: RT-PCR more than doubles the yield of detection of peritoneal disease in gastric cancer and more than triples the yield in pancreatic cancer. Using a panel of 4 markers for each diagnosis, we successfully identified all patients with stage IV disease. The prognostic implications of PCR+ / cytology- status in stage II and III patients will be determined with clinical follow-up.

Stage	Gastric Cancer			Pancreatic Cancer		
	All Patients	Cytology+	PCR+	All Patients	Cytology+	PCR+
0	3	0	0	0	0	0
I	8	0	0	1	0	0
II	14	1	5	26	0	6
III	15	1	5	3	0	2
IV	10	7	10	12	6	12
Total	50	9	20	42	6	20

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Intraoperative Tumor Regression Grade (TRG) Assessment After Neodjuvant Chemoradiation Therapy for Locally Advanced Rectal Cancer V. Canzonieri, C. Belluco,* A. De Paoli, V. Belardinelli, T. Perin, R. Sigon, R. Cannizzaro, M. Lise, F. De Marchi. *CRO - National Cancer Institute, Aviano, Italy.*

Introduction: The treatment of locally advanced rectal cancer by full-thickness transanal excision following neoadjuvant chemoradiation therapy pathological response is under investigation in clinical studies. In view of a single-step surgical procedure approach, we explored the possibility of assessing rectal cancer chemoradiation tumor regression grade (TRG) by intraoperative frozen section. Methods: A systematic pathologic analysis of Bouin-fixed paraffin-embedded sections of rectal cancers treated by neoadjuvant chemoradiation and surgery at our Institution between 1996 and 2007 was carried out. The concordance between the TRG assessed by pathologic analysis of the central tumor section (the section which could be potentially used for intraoperative frozen section analysis), and the TRG assessed by pathologic analysis of the entire tumor volume was evaluated. Results: A total of 924 tumor sections from 132 rectal cancers were examined (mean number of sections per tumor = 7). Surgical treatment was transanal local excision in 31 cases, low anterior resection in 86 cases and abdominoperineal resection in 15 cases. Concordance between the TRG assessed in the central section and in sections representative of the entire tumor volume was 92.4 % (95% CI: 87.9 – 96.9). In discordant cases TRG changed from 1 to 2 in 3 cases, from 1 to 3 in 2 cases, from 2 to 3 in 3 cases, and from 3 to 4 in 2 cases. In concordant cases a trend toward a higher percentage of cancer cells distribution in the central sections compared to the peripheral sections was observed. Conclusions: Our data sets the rationale for prospective evaluation of intraoperative TRG assessment accuracy. This strategy should be explored since it has the potential to reduce the number of two-step surgical procedures after neodjuvant chemoradiation therapy for locally advanced rectal cancer.

Table: Tumor Regression Grade (TRG) assessed by pathological analysis of the central tumor section and of the entire tumor volume in 132 rectal cancers treated by neoadjuvant chemoradiation

TRG	Central section	Entire tumor volume
1	56	51
2	21	21
3	33	36
4	17	19
5	5	5

P60

Feasibility of synchronous resection of primary and metastatic carcinoid tumors A.S. Caudle,* E.K. Abdalla, K. Willborn, J.N. Vauthey, D.B. Evans, L.M. Ellis, J.C. Yao, S.A. Curley. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Background: Surgical management for metastatic carcinoid tumors can provide symptom relief and disease control. The purpose of this study was to determine the safety and efficacy of synchronous primary bowel and liver resection for metastatic carcinoid. Methods: We retrospectively reviewed medical records of patients undergoing synchronous liver and bowel resection for metastatic carcinoid between 1999-2007 to determine clinical and surgical information. Results: Twenty-four patients were treated. The median age was 57.5 years and median follow-up was 29 months (range 1-89). Nineteen presented with carcinoid syndrome. Liver resections included right or left hepatectomy (9), hepatectomy plus wedge resection (WR) (2), extended hepatectomy (3), bisegmentectomy (3), bisegmentectomy with WR (1), and WR only (5). Radiofrequency ablation was also performed in 8 patients. Four patients had R0 resections; residual disease in the remaining patients was located in the liver (18), mesenteric nodes (3), and lung (1). Median hospital stay was 8 days (range 5-14). Eight patients (33%) had postoperative complications including abdominal fluid collections drained percutaneously (4), pleural effusions requiring drainage (3), dehydration (1), line sepsis (1), enterocutanuous fistula (ECF) (1), and portal vein thrombosis managed with anticoagulation (1). One patient required laparotomy to repair an ECF. There were no deaths. In patients presenting with carcinoid syndrome, 95% (18/19) had symptom improvement or resolution, while one with residual lung, liver, and mesenteric disease had persistent carcinoid symptoms. At last follow-up, all patients are alive; 4 (17%) are alive without evidence of disease at median 13 month follow-up (range 5-45); 20 (83%) are alive with disease at median 31 months (range 1-89). Conclusion: Simultaneous resection of primary bowel carcinoid tumors and liver metastasis can be performed safely. Surgical management offers relief of carcinoid syndrome as well as the potential for long-term disease control.

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Satisfactory long-term oncological results but relevant morbidity after preoperative chemoradiotherapy for mid-low rectal cancer: a single institution experience with a median follow-up of 7 years

S. Pucciarelli,[1]* G. Gagliardi,[1] P. Toppan,[1] L. Pasetto,[2] M.L. Friso,[3] M. Briarava,[1] D. Nitti.[1] *1. Dipartimento di Scienze Oncologiche e Chirurgiche. Clinica Chirurgica II. University of Padova, Padova, Italy; 2. Istituto Oncologico Veneto. IRCCS Padova. Sezione di Oncologia, Padova, Italy; 3. Istituto Oncologico Veneto. IRCCS Padova. Sezione di Radioterapia, Padova, Italy.*

Purpose. To evaluate the long-term outcome and late complications after preoperative chemoradiotherapy (pCRT) for rectal cancer. Methods. Data of patients undergoing surgery for rectal cancer was prospectively collected since 1994. Inclusion criteria were: primary rectal adenocarcinoma located up to 11 cm from the anal verge (AV); pre-treatment TNM stage II III (assessed by pelvic CT and/or TRUS); age 18-80 yrs; minimum follow-up >48 months; radiotherapy administered by conventional fractionation with total dose >40 Gys, and concomitant 5-FU-based chemotherapy. Late complications were defines as occurring > 6 months after surgery. Survival was calculated using the Kaplan-Meier method. Results. Our study population was of 126 patients (M:F = 80:46; median age: 60 yrs). Median distance of the tumor from the AV was 6 cm (range 1-11). Pre-treatment TNM stage was II (n=45), and III (n= 81). Although a sphincter-saving procedures was performed in 111 (88%) patients, at the last follow-up only 78% were stoma-free. R0-1 procedures were performed in 115 (91%) cases. The rate of pathologic complete response was 16% (n=20).At a median follow-up of 86 (range 54-160) months, the 5 and 10-year overall survival was 75% and 66% respectively and disease free survival 82% and 80% respectively. Of 115 patients after an R0-1 resection 21 (18%) had recurrence (local only, n=1; local and distant, n=4; distant only, n=16). Of them 20 occurred within 48 months of follow-up. Late complications occurred in 44 (35%) patients. Seven (6%) were clearly radiation-related (ureteric stricture n=4; pelvic fractures n=2; rectovaginal fistula, n=1) and were significantly associated with higher radiation dose (p=0.0004). Among the other complications the most frequent were laparocele (17%) and persistent anastomotic stricture (6%). Overall 19 (15%) patients required surgery because of late complications. Conclusion. Despite satisfactory oncological outcome, late morbidity after pCRT is relevant. Most recurrences (95%) were found within four years from surgery.

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Relapse after curative resection for colorectal cancer; time to relapse and outcome: A Japanese multicenter study H. Kobayashi,[1]* H. Mochizuki,[2] K. Sugihara.[2] *1. Department of Surgical Oncology, Tokyo Medical and Dental University, Tokyo, Japan; 2. The Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) on Postsurgical Surveillance of Colorectal Cancer, Tokyo, Japan.*

INTRODUCTION: Relapse after curative resection for colorectal cancer occurs at a constant rate. However, the association between time to relapse and prognosis after relapse is still unclear. The aim of this multicenter study was to clarify the outcomes according to time to relapse after curative resection for colorectal cancer. **METHODS:** We collected 5230 consecutive patients who underwent curative resection for colorectal cancer at 14 hospitals from 1991 to 1996. All patients were followed up intensively. Time to relapse was classified into 3 groups as follows: group A; time to relapse≤1 year, group B; 1 year < time to relapse≤3 years, group C; 3 years < time to relapse. The prognoses after relapse were compared among 3 groups by the metastatic site. **RESULTS:** Of the 5230 patients, 906 developed relapse (17.3%). The median follow-up period was 6.6 years. In total, the resection rates for relapse with curative intent were 35.2% in group A, 46.6% in group B, and 45.1% in group C (p = 0.0045). There were significant differences in prognoses after relapse among 3 groups in liver (p = 0.0175) and local relapse (p = 0.0021). However, in each recurrent site, there were no significant differences in the prognoses among 3 groups, when they underwent resection for relapse with curative intent. **CONCLUSIONS:** The later the relapse, the more the resection with curative intent. On the other hand, time to relapse did not affect the outcomes after curative resection for relapse. It is important to detect relapses in resectable condition regardless of time to relapse. It is necessary to validate that the intensive surveillance after curative resection for colorectal cancer can improve the curative resection rate for relapses and the prognoses.

Time to relapse and resection rate with curative intent

Recurrent site	Tiem to relapse (TR)	Patients with curative resection for relapse	Patients without resection for relapse	Total number of relapse	Resection rate (%)	p value
Liver		172	201	373	46.1	
	≤1 year	71	117	188	37.8	
	1 year< ≤3 years	80	60	140	57.1	0.0023
	3 years<	21	24	45	46.7	
Lung		95	155	250	38.0	
	≤1 year	24	58	82	29.3	
	1 year< ≤3 years	43	70	113	38.1	0.038
	3 years<	28	27	55	50.9	
Local		78	131	209	37.3	
	≤1 year	21	53	74	28.4	
	1 year< ≤3 years	40	55	95	42.1	0.14
	3 years<	17	23	40	42.5	
Anastomosis		15	7	22	68.2	
	≤1 year	4	3	7	57.1	
	1 year< ≤3 years	10	4	14	71.4	0.63
	3 years<	1	0	1	100	

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Is adjuvant chemotherapy necessary for T1 stage III colorectal cancer? S. Ishiguro,* S. Yamamoto, S. Fujita, T. Akasu, Y. Moriya. *National Cancer Center Hospital, Tokyo, Japan.*

Background: Adjuvant chemotherapy is the standard of treatment for stage III colorectal cancer. However, the efficacy of adjuvant chemotherapy for patients with T1 stageIII colorectal cancer is not fully assessed. The purpose of this study is to investigate outcome of patients with T1 colorectal cancer undergoing radical surgery and to identify the candidates who are likely to benefit from adjuvant chemotherapy. **Methods**: Between 1963 and 2003, patients with T1 colorectal cancer undergoing radical surgery were investigated retrospectively. Patients who had history of cancer, synchronous advanced colorectal cancer, familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer were excluded. Primary endpoint was recurrence-free survival (RFS). Of 670 patients analyzed, RFS and factors predictive of decreased RFS were investigated. **Results**: Lymph node involvement was confirmed in 74 patients (11%). Of the 74 patients, adjuvant chemotherapy was administered in 7. RFS rates at 3 years were 96% in node negative patients and 89% in node positive patients. By multivariable analysis, patients who had carcinoembryonic antigen (CEA) level of ≥5.0 ng/dl (RR = 2.85, 95% CI = 1.64-4.96) and who have ≥3 lymph node involvements (RR = 4.14, 95% CI = 1.60-10.72) had significantly decreased RFS. Adjuvant chemotherapy did not have influence on RFS. RFS in patients having one or two lymph node involvements did not differ compared to that of node negative patients (RR = 1.35, 95% CI = 0.64-2.86). By subset analysis stratified by tumor location, CEA level of ≥5.0 ng/dl is the sole determinant of decreased RFS for colon cancer. For rectal cancer, CEA level of ≥5.0 ng/dl and ≥3 lymph node involvements were associated with decreased RFS. **Conclusions**: Patients with T1 stage III colorectal cancer having one or two lymph node involvements have favorable RFS and could avoid adjuvant chemotherapy. Patients with CEA level of ≥5.0 ng/dl or with have ≥3 lymph node involvements are absolute candidates for adjuvant chemotherapy, particularly in rectal cancer. These results need to be confirmed and validated in another dataset.

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Factors Influencing the Number of Lymph Nodes Retrieved After Gastrectomy for Gastric Adenocarcinoma S.J. Schoenleber,* T. Schnelldorfer, C.M. Wood, R. Qin, M.G. Sarr, J.H. Donohue. *Mayo Clinic College of Medicine, Rochester, MN.*

INTRODUCTION: For patients with resectable adenocarcinoma of the stomach, regional lymph node metastases are one of the most important predictors of survival. Currently, 15 lymph nodes must be examined for accurate AJCC/UICC staging. In the western hemisphere, the number of lymph nodes examined is frequently less than this standard. Clinical factors correlating with the number of lymph nodes examined are poorly understood and may be amenable to relatively easy changes. METHODS: We performed a retrospective chart review of a series of 99 consecutive patients who underwent gastrectomy for gastric adenocarcinoma distal to the gastroesophageal junction at a large tertiary care facility. Clinical variables that correlated with the number of lymph nodes retrieved were analyzed. RESULTS: Ninety-nine patients underwent gastrectomy for adenocarcinoma of the stomach at our two hospitals. More than 15 lymph nodes were examined in 64% of specimens. Univariate analysis showed a correlation between number of lymph nodes retrieved and number of positive lymph nodes ($p<0.001$), extent of lymphadenectomy (D1: 19.1±14.0 LN vs. D2: 30.5±19.8 LN; $p<0.001$), hospital where the operation was performed (Hospital A: 38.4±21.8 vs. Hospital B: 18.5±11.8; $p<0.001$), surgeon performing the procedure (Surgeon A: 42.1±17.3, Surgeon B: 19.7±12.5, Surgeon C: 22.4±11.5, Surgeon D: 11.2±7.1, Others at Hospital A: 27.3±30.7, Others at Hospital B: 19.7±12.2; $p<0.001$), and pathology technician preparing the specimen (Tech A: 50.3±21.1, Tech B: 13.4±8.7, Other: 21.1±11.6; $p<0.001$). Multivariate analysis identified the pathology technician as the only independent staff-related variable contributing to the variation of number of lymph nodes, using both fixed ($p<0.001$) and random effects models. CONCLUSION: This study indicates that the only staff-related factor in our center influencing lymph node retrieval after gastrectomy for gastric adenocarcinoma is the pathology technician. In identifying potential areas benefiting from a systems improvements approach, focus on the technical aspects of processing the specimen would be of greatest benefit.

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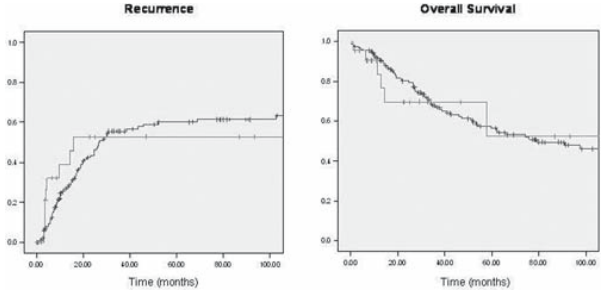
Does surgical technique affect recurrence and survival in patients undergoing resection of colorectal liver metastases? A. Bonavia,* U. Sarpel, A. Grucela, S. Roayaie, M.E. Schwartz, D.M. Labow. *Mount Sinai School of Medicine, New York, NY.*

INTRODUCTION: Some have postulated that anatomic resection of colorectal liver metastases (CLM) may offer a survival advantage because 1) this method removes the functional hepatic unit as a whole and 2) nonanatomic hepatic resection has been reported to have a higher incidence of positive surgical margins. METHODS: A retrospective review was performed of all patients undergoing hepatic resection for CLM from 10/01/87-8/01/07. 183 patients met inclusion criteria of undergoing either anatomic or nonanatomic resection with the aim of removing all gross disease. Positive margin status was defined as the presence of tumor within 1mm or less of the cut margin. RESULTS: The mean age was 61 years (range 31-90) with 57% being male. 89 patients (49%) underwent nonanatomic resection, the remaining 94 (51%) had anatomic resection. Average duration of inflow occlusion was 10 minutes. The average length of stay was 7.4 days. There were 3 deaths, yielding a 1.6% 30-day mortality rate. Overall, there was a 14% (n=22) positive margin rate, with no difference between anatomic and nonanatomic resections. The risk of recurrence was 28%, 55% and 59% at 1, 3, and 5-years respectively. Overall survival was 89%, 67%, and 55% at 1, 3, and 5 years respectively. Positive margins were not associated with a higher recurrence rate or shorter survival. Type of resection (anatomic or nonanatomic) was not associated with significant differences in recurrence rates or overall survival. As previously described in the literature, transfusion is highly correlated with poorer survival ($p=0.001$). CONCLUSION: Hepatic resection for CLM can be performed safely and offers select patients with Stage IV colorectal cancer prolonged survival. Margin status appears to be less important than previously reported, perhaps due to newer, more effective chemotherapy regimens. Therefore, the choice of anatomic or nonanatomic resection should be dictated by the number and location of tumors, rather than based on oncologic principles. An emphasis on the preservation of hepatic parenchyma may be of increasing importance with the growing awareness of chemotherapy-associated steatohepatitis.



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Postoperative Mortality following Esophagectomy for Cancer: Development of a Risk Prediction Model utilizing the SEER-Medicare Database E.C. Paulson,* J. Ra, C. Wirtalla, K. Armstrong, J. Kucharczuk, R. Kelz, F. Spitz. *Hospital of the University of Pennsylvania, Philadelphia, PA.*

Introduction: Surgical resection for esophageal cancer remains a high risk endeavor. We sought to identify factors associated with postoperative mortality for patients undergoing esophagectomy for cancer in order to develop a model to predict risk of postoperative death. **Methods:** We performed a retrospective cohort study of patients in the SEER-Medicare database who underwent esophagectomy for cancer from 1997-2002. Multivariate logistic regression was performed to evaluate the relationship between preoperative patient and provider characteristics and postoperative mortality. Using significant variables from the regression, a simple, clinically applicable model was developed to predict patient risk for postoperative mortality. **Results:** 1225 patients in the SEER-Medicare files underwent esophagectomy for cancer from 1997-2002. Overall, postoperative mortality in this cohort was 14%. Logistic regression demonstrated that age, Charlson score (comorbidity index), and hospital volume were significant predictors of postoperative mortality. The odds of postoperative mortality at low volume hospitals were twice those at high volume centers. Age greater than 80 increased odds of mortality almost two-fold. Similarly, Charlson scores of 2+ resulted in a one-and-a-half fold increased risk of postoperative death. Utilizing these significant variables, we developed a weighted points system to predict postoperative mortality. Points were assigned based on a patient's age and Charlson score and on hospital surgical volume. As demonstrated in table 1, this model demonstrated a direct relationship between the calculated score and postoperative mortality and effectively stratified patient risk of postoperative death. **Conclusion:** Despite advances in intraoperative technique and postoperative care, mortality following esophagectomy remains comparatively high. Using this scoring system, referring physicians or surgeons can readily and accurately predict a patient's risk of postoperative mortality. This will allow physicians and patients to make informed decisions about the role and the best environment for surgical treatment.

Table 1: Post-operative Mortality Predictive Model

1 Point Age 70-79	**2 Points** Age 80+ Low or Medium Volume Charlson ≥2
Preoperative Risk Score [1]	**Observed Mortality (%)**
0	4
1	10
2	12
3	15
4	20
5+	24

[1] Individual patient scores are calculated by the summation of all risk factor points

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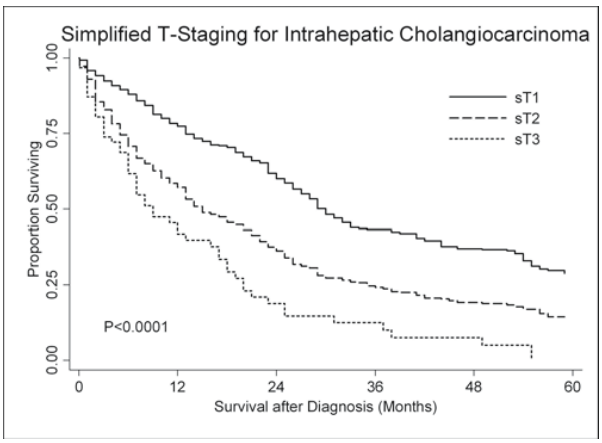
A Simplified Staging System for Intrahepatic Cholangiocarcinoma
H. Nathan,[1]* T. Aloia,[2] J.N. Vauthey,[3] E.K. Abdalla,[3] D. Zorzi,[3] R.D. Schulick,[2] M.A. Choti,[1] T.M. Pawlik.[1] *1. Johns Hopkins, Baltimore, MD; 2. The Methodist Hospital, Houston, TX; 3. The University of Texas M. D. Anderson Cancer Center, Houston, TX.*

Introduction: The current American Joint Committee on Cancer (AJCC) staging system for intrahepatic cholangiocarcinoma (ICC) is identical that for hepatocellular carcinoma (HCC). The staging system is based, however, on data exclusively derived from HCC patients (pts) and thus may be inappropriate for pts with ICC. We sought to empirically derive an ICC staging system from population-based data of pts undergoing surgery for ICC. Methods: The Surveillance, Epidemiology and End Results (SEER) database was used to identify 647 pts who underwent cancer-directed surgery for ICC between 1988-2004. The ability of the current AJCC staging system to stratify ICC pts was examined and independent predictors of survival were identified using Cox proportional hazards models. Results: Median tumor size was 5.0 cm. Most pts had a solitary tumor (72%), no evidence of vascular invasion (67%), and no lymph node metastases(N0)(72%). Median survival was 21 mon and 5-yr survival was 18%. Using the current AJCC T classification, pts with T2 and T3 tumors had similar 5-yr survivals (15% vs. 14%, respectively;p=0.22). The inability of the current T2 and T3 classifications to adequately stratify ICC pts was due to tumor size >5 cm not being a relevant prognostic factor (HR=1.01;p=0.92). In contrast, multiple lesions (HR=1.63;p=0.001) or vascular invasion (HR=1.54;p=0.01) was associated with an adverse prognosis. Based on these findings, a simplified ICC T-staging system was developed: T1-single liver lesion, no vascular invasion; T2-multiple liver lesions and/or vascular invasion; T3-extrahepatic extension (p<0.0001)(Figure). 5-yr survival was worse for pts with N1 (7%) vs. N0 (25%) disease. As such, a revised ICC stage grouping system was proposed: stage I: T1, N0, M0; stage II: T2, N0, M0; stage III: T3, N0, M0 or any T, N1 M0; stage IV: any T, any N, M1 (overall p<0.0001). Conclusions: The current AJCC T-staging system for ICC fails to stratify pts adequately. The system is unnecessarily complex as it includes tumor size, which provides no additional prognostic information. We propose a simplified system of stratification that is based on number of tumors, vascular invasion, nodal status, and metastatic disease.



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ROLE OF HEPATIC RESECTION IN PATIENTS WITH BREAST CANCER LIVER METASTASES
P.L. Pilati,[1]* S. Mocellin,[1] E. Mammano,[1] S. Corazzina,[1] G. Arman,[1] M. Lise,[2] D. Nitti.[1] *1. Clinica Chirurgica 2, University of Padova, Padova, Italy; 2. Department of Surgery, CRO–IRCCS, National Cancer Institute, Aviano (PN), Italy.*

Background: Patients with liver metastases from breast cancer have poor survival (median survival 3-6 months). The only curative treatment is hepatic resection, unfortunately feasible in only 3-5% of patients. The purpose of this study is to examine our experience with hepatic resection in patients with breast cancer liver metastases. Methods: We considered 29 patients with metachronous breast cancer liver metastases treated with hepatic resection from 1986 to 2006. Clinical and pathological data from breast and hepatobiliary database were reviewed and correlated with overall survival and disease free survival. Results: Mean age of the patients was 53 years (range 30-71). Twenty-six (89.6%) patients received preoperative systemic chemotherapy, while 21 (72.4%) received preoperative and postoperative systemic chemotherapy. Liver metastases were solitary in 24 patients (82.7%) and multiple in 5 patients (17.3%). Six patients were treated with major hepatectomy (≥ 3 segments) and 23 with minor hepatectomy (< 3 segments); no postoperative mortality occurred. Microscopically positive margins (R1) were present in 7 (24.1%) patients. At a mean follow-up of 37 months after hepatic resection, median survival was 32 months. The overall 1-, 2- and 5-years survival rates were 83%, 60%, 20% respectively. The only study variable independently associated with poor survival rates was the presence of positive resection margins (R1) (P = 0.04). Conclusions: Hepatic resection may achieve a significant survival benefit in selected patients with breast cancer liver metastases (no extrahepatic disease, probable R0 resection). Considering our results and the literature, we suggest to consider surgery more frequently in the multimodality treatment of breast cancer liver metastases.

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Defecatory Function and Quality of Life after Rectal Cancer Surgery
M. Ishiguro,[1]* Y. Hashiguchi,[2] H. Ueno,[2] H. Mochizuki,[2] K. Sugihara.[1] *1. Tokyo Medical and Dental University, Graduate School, Department of Surgical Oncology, Tokyo, Japan; 2. National Defense Medical College, Department of Surgery, Saitama, Japan.*

INTRODUCTION: Patients after rectal cancer surgery suffer from disturbed defecatory function and impaired quality of life (QOL). The aim of this study is to clarify improvement of the function and QOL with time, and investigate when they are stabilized. METHODS: The questionnaire was mailed to a total of 320 patients without recurrence who had undergone curative surgery for rectal cancer since January 2000 to December 2006. The questionnaire about defecatory function includes Wexner's incontinence score, and the questions about holding, fragmentation and use of laxative. QOL was evaluated by using SF-36v2. RESULTS: The 233 respondents were studied (response rate: 72.8%). There were 54 cases of high anterior resection (HAR), 82 of low anterior resection (LAR), 51 of ultra-low anterior resection (U-LAR), and 46 of abdominoperineal resection (APR). The median follow-up time was 1081 days. Continence was worse with shorter distance from the anal verge (AV) to the tumor. Continence of the patients after U-LAR was significantly worse than that after LAR and HAR (Wexner's score, 8.1 vs. 3.1and 0.9; p<0.001). Continence was improved with time up to 2 years after surgery, but improvement after 2 years was not observed. Patients after LAR showed good continence (Wexner's score < 5) in 2 years after surgery, while the continence of the patients after U-LAR even after 2 years was significantly worse than that of LAR (Wexner's score, 2.4 vs. 7.1; p<0.001). In the patients with lower rectal cancer (< AV 6cm), the patients underwent transanal anastomosis showed no improvement of their continence, while ones underwent double-stapling anastomosis showed improvement with time up to 2 years after surgery. And 90% of the patients suffered from fragmentation even after 2 years. There was no difference in scores of each domain of SF-36v2 between APR and LAR. CONCLUSIONS: Defecatory function after anterior resection was improved with time up to 2 years after surgery, but the distance from AV to the tumor influenced the improvement of the function. QOL after APR did not differ from that after LAR. For the better acceptance for the postoperative life, these informations should be provided to the patients.

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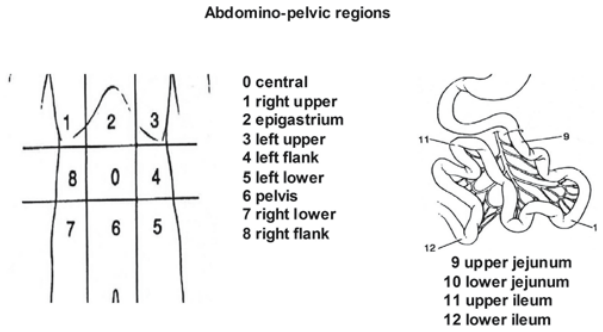
Diffuse Malignant Peritoneal Mesothelioma: Analysis of Treatment Failure Following Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy
D. Baratti,* S. Kusamura, B. Laterza, M. Deraco. *surgery, istituto nazionale tumori, milano, Italy.*

INTRODUCTION Improved survival has been recently reported in selected patients with diffuse malignant peritoneal mesothelioma (DMPM) undergoing cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). The issue of treatment failure has never been extensively addressed. The aim of this study was to analyze the failure pattern, management and outcome of progress-

ing DMPM following comprehensive treatment. METHODS Prospectively collected data regarding 40 patients with progressive DMPM from a total of 74 undergoing cytoreduction and HIPEC were reviewed. The failure pattern was analyzed in terms of progressive disease distribution in 13 abdominopelvic regions (see figure). Fourteen patient, tumor and treatment-related factors were investigated for possible correlation to the failure pattern. Clinicopathological variables predicting survival from progression were assessed by multivariate analysis. RESULTS Median time to progression was 9 months (range 2-81) and median survival from progression 8 months (range 1-86). The failure pattern was diffuse involvement of small bowel in 27 patients, intra-abdominal involvement exclusive of small bowel in 6, isolated pleural involvement in 3, concurrent abdominal and pleural spread in 2 and undetermined in 2. Among the tested factors, only the completeness of cytoreduction correlated to disease progression in the following regions: upper jejunum (multivariate [m] P=.013), lower jejunum (mP=.004), upper ileum (mP=.002), epigastrium (mP=.001). Disease progression was treated with 2nd cytoreduction and HIPEC in 4 patients, surgical debulking in 6, systemic chemotherapy in 15, supportive care in 15. Time to progression ≤9 months (mP=.009), poor performance status (mP=.005), supportive care (mP=.003) correlated to reduced survival from progression. CONCLUSION Progressive DMPM following comprehensive treatment mostly remained confined to the abdomen. Incomplete cytoreduction in anatomical sites where tumor removal is technically difficult is a leading cause of treatment failure. In selected patients, aggressive treatment for postoperative progression seems worthwhile.



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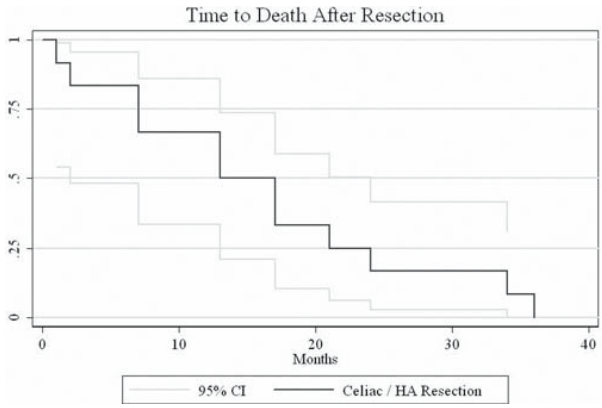
Survival after pancreatectomy with major arterial resection and reconstruction K.B. Stitzenberg,* J.C. Watson, S.J. Cohen, A.A. Konski, J.P. Hoffman. *Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Absence of major arterial tumor involvement has generally been regarded as one of the criteria for resectability of pancreatic tumors. We hypothesize that resection of a tumor-involved hepatic artery (HA) or celiac axis with arterial reconstruction may offer a survival benefit to patients whose tumors were traditionally regarded as unresectable. Methods: All patients with pancreatic cancer treated at our institution between 1998 and 2007 were reviewed. Patients were included in the study if they underwent resection of the HA or celiac axis at the time of operation. Survival was analyzed using standard Kaplan-Meier survivor function and Cox proportional hazards models. Results: 12 patients (6 male, 6 female) underwent pancreatic resection with HA and/or celiac axis reconstruction for pancreatic adenocarcinoma. The median age at diagnosis was 62 years (range 53-73 years). All patients successfully completed neoadjuvant chemoradiotherapy prior to resection. Procedures performed were 8 extended pancreaticoduodenectomies, 2 extended distal pancreatectomies, and 2 total pancreatectomies. Ten cases involved celiac resections, and 2 had isolated HA resections. 60-day mortality was 17% (2/12). Median survival after diagnosis was 20 months (range 6-41 months). Median survival after resection was 17 months. Figure 1. Survival was not significantly related to age, gender, margin status, or pre-operative CA19-9 level. 3-year survival from time of diagnosis was 17%; however, there were no 5-year survivors. Conclusions: Resection of the HA or celiac axis with arterial reconstruction may prolong survival for selected patients who undergo pancreatic resection after neoadjuvant therapy. However, this aggressive approach did not result in any long-term survivors in our series.



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Underutilization of surgical resection in minorities with pancreatic cancer: a national survey M.M. Murphy,* J.P. Simons, T.P. McDade, J.S. Hill, J.T. McPhee, M.E. Sullivan, G.F. Whalen, J.F. Tseng. *surgery, University of Massachusetts Medical School, Worcester, MA.*

Introduction: Among patients with pancreatic cancer, survival has been noted to vary by race. Analyses of disparities are necessary in order to close this gap in patient outcomes. We examined the effect of race on resection rates and survival. Methods: A retrospective cohort of 40,495 patients diagnosed with pancreatic adenocarcinoma was obtained from the Surveillance, Epidemiology, and End Results (SEER) registry 1992-2002. To assess the utilization of surgical resection, predictors of resection on univariate analysis were used in a multivariate logistic regression. A Cox proportional hazards model was constructed to assess predictors of overall survival, including resection status. Results: 82.0% of patients were White; 11.3% were Black; 6.3% were Other (American Indian/Alaska Native/Asian/Pacific Islander). 28.1% of patients underwent pancreatic resection (28.7% of Whites vs 26.6% of Blacks (chi-square, p<.0001)). In an analysis of stage, 6.9% of patients had localized disease; 27.6% had regional disease. Blacks were younger than Whites overall, and Blacks who underwent surgical resection were younger than Whites who underwent resection (p<.0001). By logistic regression, Blacks had an adjusted odds ratio (AOR) for resection of 0.847 (95% CI 0.789-0.910) compared to Whites. Other non-Whites had an AOR for resection of 0.715 (95% CI 0.649-0.788). The Cox model for patient survival yielded the significant covariates of male sex (HR 1.114; 95% CI 1.090-1.138), age (per year HR 1.017; 95% CI 1.016-1.018), Black race compared to Whites (HR 1.107, 95% CI 1.072-1.143), and resection (HR 0.943; 95% CI 0.921-0.965). The HR for other non-Whites was 0.942 (95% CI 0.903-0.983). Conclusions: Our analyses demonstrate that Blacks and other non-Whites with pancreatic cancer have a decreased rate of resection after adjustment for covariates including sex, age, and stage. Furthermore, Blacks have a decreased adjusted overall survival. Given the lack of recent advancement in pancreatic cancer chemotherapy, ensuring that eligible patients receive recommended care, including surgical resection if appropriate, may be one of the most effective means of improving overall survival.

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Resection of Hepatic Metastases Before the Colorectal Primary: An Alternate Treatment Strategy for Synchronous Disease
M.M. Mortenson,* S.A. Curley, J.N. Vauthey, K. Beaty, E.K. Abdalla. *M.D. Anderson Cancer Center, Houston, TX.*

Introduction: Colorectal liver metastases (CLM) are typically resected after the primary tumor. However, in selected patients with synchronous CLM, systemic chemotherapy and hepatic metastasectomy before primary resection may be appropriate. The purpose of this study was to evaluate the short-term outcomes in these patients and to identify appropriate selection criteria. Methods: A prospective database of 159 patients presenting with CLM and an intact primary (11/99 to 6/07) was reviewed. Results: CLM were resected in 26 (16%) patients before primary disease because of CLM characteristics, response of the primary tumor to systemic therapy, or more recently, as a planned strategy.

Median patient age was 50 years (34-77). Bilobar disease was present in 13 (50%) patients. The median number of CLM was 5 (1-12) with an average size of 4.5 cm. All but one patient received chemotherapy before surgery, and 88% underwent major hepatectomy. Morbidity and mortality of hepatic resection were 31% and 4%, respectively. At analysis, 15 primary tumors had been resected, 3 patients are receiving chemoradiation therapy to the primary, 6 had disease progression/death, and 2 had complete endoscopic and radiographic resolution of their primary. Of patients who completed all planned therapy, the resectability rate was 67%. Patients who did not proceed to primary resection (n=5) were more likely to have no response to chemotherapy than those who completed therapy (n=16) (p=0.02), and had a higher incidence of extrahepatic metastases (p=0.03), but did not differ for any other prognostic factor. At a median follow-up of 362 days (20-1656), 18 (69%) patients developed new metastatic disease (liver-only in 19%).The median survival of the entire study group is 38.5 months. For those who completed therapy, median survival is 54 months; 5 (31%) patients are alive with disease while 7 (44%) are disease-free. Conclusion: Resection of CLM before the primary tumor may be appropriate in patients with asymptomatic primary tumors who respond to preoperative chemotherapy and have no extrahepatic disease. This approach is not associated with increased morbidity or mortality.

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Female Sex and Standardized Mitomycin-C Dose are Associated with Increased Risk of Neutropenia after Hyperthermic Intraperitoneal Chemotherapy L.A. Lambert,[1]* T.S. Armstrong,[1] J.J. Lee,[1] L. Suyu,[1] M.H. Katz,[1] R.A. Wolff,[1] C. Eng,[1] M.L. Smith,[1] S. Gonzalez-Moreno,[2] P.F. Mansfield.[1] *1. Surgical Oncology, UT-M.D. Anderson Cancer Center, Houston, TX; 2. Centro Oncológico MD Anderson International España, Madrid, Spain.*

Background: Use of hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of peritoneal-based malignancies is increasing. Depending on treatment regimen, neutropenia is a common and potentially life-threatening early postoperative complication of HIPEC. However, little is known about the incidence or risk factors associated with HIPEC-induced neutropenia. Methods: From January 1993 to October 2006, 120 surgical cytoreduction and HIPEC with mitomycin-c (MMC) procedures were performed in 117 patients with appendiceal neoplasm. Neutropenia was defined as an absolute neutrophil count of < 1,000/uL. Variables assessed as potential risk factors for HIPEC-induced neutropenia included: age, sex, weight, BMI, BSA, splenectomy, dose of MMC (standardized for BSA and nonstandardized), percent of perfusate recovered, length of surgery, estimated blood loss, perioperative blood transfusion, and history of prior chemotherapy. Results: Patients received between 37.25 and 65 mg MMC total perfusate dose. The overall incidence of neutropenia was 39.2%. Of the 47 patients who developed neutropenia, 34 were female (72%). Female sex, BMI, BSA, and the standardized dose of MMC were significantly associated with an increased risk of neutropenia by univariable logistic regression. Female sex and standardized dose of MMC remained statistically significant for an increased risk of neutropenia on multivariable logistic regression. The odds ratio (OR) of neutropenia for females was 2.81 (95% CI: 1.08, 7.29); the OR for a one unit increase in standardized MMC dose was 1.25 (95% CI: 1.01, 1.53). No other variables were identified as independent predictors of increased or decreased risk of neutropenia. Conclusion: Neutropenia is a common complication after HIPEC with MMC. Female patients are at significantly increased risk for this complication. Risk of neutropenia also increases with MMC dose standardized for BSA. With increasing interest in the use of HIPEC for other peritoneal-based malignancies, understanding the risk factors for HIPEC-induced neutropenia may facilitate reducing the morbidity associated with this procedure.

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EVALUATION OF SURGICAL TREATMENT FOR pT2 GALLBLADDER CANCER (GC) IN CHILE J.M. Butte, E. Waugh, M. Meneses, H. Parada, H. De La Fuente*.* *Instituto Oncológico Fundación Arturo López Pérez, Santiago, Región Metropolitana, Chile.*

INTRODUCTION:GC is the most common cause of cancer mortality in chilean women and a minority of patients(pts) are diagnosed with pT2 stage. The aim of this study was to evaluate the survival of pts with surgically managed pT2 GC. METHODS:A prospective study was performed. Between 1999 and 2007, pT2 GC was diagnosed during or after cholecystectomy in 25 pts who underwent resection. Preoperative studies included laboratory analyses and abdominal CT scan. In cases of incidental diagnosis(ID) a review of the biopsy was carried out to confirm the depth of tumor invasion. All patients were staged according to 2002 AJCC TNM system. R0 resection(R0R) included the gallbladder, segments IVB and V of the liver, regional lymph node(LN) dissection (cystic, pericoledochal, common hepatic artery and intercavoaortic(ICA)) and common hepatic bile duct resection(rCHBD) when positive cystic duct margin(PCDM) was found. RESULTS:The series included 19 women and 6 men with a mean age of 56 (41-72)years. Twenty pts had an ID of GC; all of whom underwent re-exploration. In 16 pts a R0R was achieved while in 9 pts a R1-R2 resection(R1-R2R) was performed. One patient developed a postoperative collection treated without reoperation. No mortality was observed. The reasons for R1-R2R were: liver metastases in 3, positive ICA LN in 3 and carcinomatosis in 3. In pts undergoing R0R: 5 were positive LN, 3 had tumor involvement of the gallbladder bed, and 2 had PCDM which prompted a rCHBD. In R0R, the mean number of LN positive/resected were 0.8/9.7, respectively. For the entire group, the 5 year overall survival and the median survival(MS)were 21% and 20 months(m), respectively. The MS of R0R pts compared to R1-R2R pts was 21.8 vs. 12.6 m (p=0.02). In the group of pts treated with R0R, those with negative LN had improved MS compared to pts with positive LN (24.5 vs. 7.4 m). MS of the pts with ID versus intraoperative diagnosis(IOD) were 22.5 and 7.3 m, respectively. CONCLUSION:Patients with pT2 GC and negative preoperative imaging are likely to have additional intraabdominal tumor. IOD of GC is associated with more advanced disease and worse prognosis than ID. R0R and N0 disease are associated with improved survival.

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Does body mass index affect perioperative outcomes after esophagectomy for cancer? M. Melis,[1]* J.M. McLoughlin,[2] E.M. Dean,[1] E.M. Siegel,[1] J. Weber,[1] S.T. Kelley,[1] R.C. Karl.[1] *1. H. Lee Moffitt Cancer Center, Tampa, FL; 2. Medical College of Georgia, Augusta, GA.*

Introduction Given the growing rate of obesity, effects of excessive body weight on surgical outcomes constitute a relevant issue. Our aim was to determine the effects of preoperative body mass index (BMI) on outcomes after esophagectomy for cancer. We also investigated if transhiatal (THE) and Ivor-Lewis esophagectomy (ILE) were associated with different morbidity in the obese patients. Methods From our esophageal database we identified obese (OB, BMI ≥ 30) and normal-weight (NW, BMI <30) patients. Incidence of pre-operative risk factors and peri-operative complications in each group were analyzed. Fisher exact and Chi square tests were used as appropriate to calculate statistical significance. Results Our database included 296 patients who underwent esophagectomy for cancer. Data on BMI was available for 273 (39 females and 234 males): 184 patients (67.3%) had NW, 89 (32.7%) were OB. NW and OB patients presented with same incidence of coronary (26% vs. 29%), peripheral (7% vs. 2%) and cerebro-vascular disease (5% vs. 6%), congestive heart disease (4% vs. 2%), renal insufficiency (2% vs. 0%), history of smoking (79% vs. 81%) or drinking (49% vs. 42%). OB patients had higher incidence of diabetes (23% vs. 9%, p=0.01), hiatal hernia (26% vs. 13%, p=0.003), gastric reflux (53% vs. 39%, p=0.008). NW had higher incidence of COPD (29% vs. 20%, p=0.03) Table 1 lists the post-operative events observed in each group. The majority of our patients (86%) had undergone ILE; incidence of overall complications was similar to THE, both in NW (54% vs. 82.4%, p=0.06) and in OB (63% vs. 80%, p=0.7). Conclusions In our population OB patients were more likely to have diabetes and gastro-esophageal reflux, but incidence of other co-morbidities was similar to NW. Overall, morbidity and mortality after esophagectomy were not affected by BMI in carefully selected surgical patients. However OB patients were more likely to suffer from post-operative reflux and showed a trend toward delayed gastric emptying; those complications were not related to pre-existing diabetes. ILE and THE were associated with similar morbidity both in NW and OB.

Table 1.

	NW N(%)	OB N (%)	p
Myocardial event	4 (2.2)	2 (2.6)	0.3
Arrhythmia	23 (12.5)	9 (11.7)	0.1
Blood transfusion	9 (4.9)	3 (3.9)	0.2
Bowel injury	1 (0.5)	0 (0)	0.6
Respiratory failure	17 (9.2)	5 (5.6)	0.1
Pneumonia	28 (15.2)	13 (16.9)	0.1
Wound infection	7 (3.8)	6 (6.7)	0.1
Prolonged ICU stay	11 (6.0)	3 (3.9)	0.1
DVT	3 (1.6)	2 (2.6)	0.3
PE	3 (1.6)	3 (3.9)	0.2
Anastomotic leak	10 (5.4)	4 (4.4)	0.2
Anastomotic stricture	19 (10.3)	12 (13.4)	0.1
Delaed gastric emptying	22 (12)	16 (17.9)	0.059
Severe post-operative reflux	23 (12.5)	18 (20.2)	0.03
Any complications	106 (57.6)	57 (64)	0.06
Mortality	3 (1.6)	4 (4.4)	0.2

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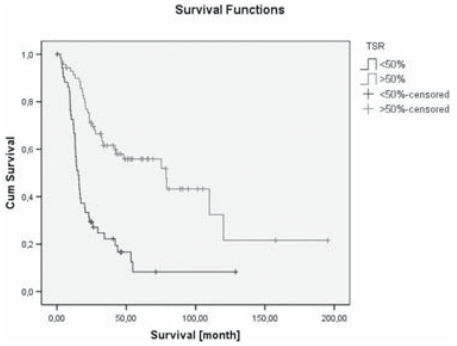
Tumour-Stroma Ratio: a Strong and Independent Prognostic Factor for Adenocarcinomas of the Esophagus M. Wouters,[1]* M. Takkenberg,[2] W. Mesker,[2] V. Smit,[2] L. Stassen,[3] H. Hartgrink,[2] R. Tollenaar.[2] *1. Surgical Oncology, the Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital, Amsterdam, Netherlands; 2. Leiden University Medical Center, Leiden, Netherlands; 3. Reinier de Graaf Hospital, Delft, Netherlands.*

Introduction: In the literature a revision of the current TNM-classification of tumours of the esophagus has been proposed. The additional prognostic value of lymph node characteristics, like the number of positive nodes, lymph node ratio and extra-capsular involvement could refine the current staging model. Only recently tumour-stroma-ratio (TSR) has been identified as a histological characteristic of the tumour itself, that proves to be a strong predictor for survival in colorectal carcinomas. The aim of this study was to evaluate the prognostic value of TSR in resected adenocarcinomas of the esophagus. Methods: In the regional cancer registry, we identified 122 consecutive patients with an adenocarcinoma of the esophagus, resected between 1990 and 2004 in two hospitals in our region. Retrospectively TSR was investigated on the original tissue sections by 4 independent pathologists, using a pre-determined histopathological protocol. Results: Using a cut-off value of 50% patients were classified as TSR high and TSR low. There were no significant differences in age, gender, tumour size and localization, between the two groups. There were also no differences in treatment characteristics. The (disease-free) survival of patients with a high TSR was significantly better than in the TSR low group (Figure 1). By multivariate analysis, TSR was identified as a highly significant prognostic factor for DFS (HR 3.3; p<0.001), as well as for OS (HR 3.6; p<0.001), independent of histological grade, tumour invasion, nodal status, -ratio or extra capsular involvement. Conclusion: TSR is a new prognostic tumour characteristic for adenocarcinomas of the esophagus that can be used to identify patients at risk for early recurrence. In addition, the role of excessive stroma production in epithelial tumours will be the subject of future research.



Overall survival after resection of adenocarcinomas of the esophagus for tumours with low-TSR (<50%) and high-TSR (>50%).

P78

Genetic Alterations in Primary Colon Cancers Associated with Lymph Node Metastasis A.A. Sarnaik,* E. Siegel, K. Meredith, S. Eschrich, J.M. McLoughlin, R. Nair, J.M. Lewis, G. Bloom, T. Yeatman, D. Shibata. *Surgical Oncology, H. Lee Moffitt Cancer Center, Tampa, FL.*

Introduction: Patients with node-negative colon cancers (NNCC) are often cured by surgical resection alone, while patients with node-positive colon cancers (NPCC) often recur despite adjuvant therapy. The genetic changes conferring aggressive tumor biology in NPCC are not well characterized. By combining microarray analysis with a comprehensive clinical database, we have sought to correlate the clinical and gene expression profiles associated with lymph node metastases. Methods: From 1993 to 2003, colon cancer specimens were collected from consenting patients. Each tumor was characterized for the expression of over 30,000 genes using the Affymetrix 133 Plus 2.0 Gene chip. Clinical data were collected by retrospective chart review. Statistical comparisons of the clinical data were performed using the Fisher Exact Test. Gene expression data were normalized and compared using the Mann-Whitney test. Results: We identified a total of 63 patients with NNCC and 37 patients with NPCC. The population comprised 49 males and 51 females with a median age of 70 years (range 27-90). Patients with nodal metastasis had a higher tumor grade (p=0.02). There were no significant differences with respect to mucin production, perineural or lymphovascular invasion. At a false discovery rate of 0.1, patients with nodal metastasis displayed 26 up-regulated genes and one down-regulated gene as compared to those without nodal metastasis. Several cancer-related genes were found to be up-regulated and have been implicated in biologic processes that would be predicted to promote nodal metastasis including: tumor dedifferentiation, immunomodulation, inhibition of apoptosis and tumor invasion (Table 1). Conclusion: Our study represents a unique comprehensive evaluation of clinical and genetic features regarding colon cancer nodal metastasis. We have demonstrated that a panel of individual genes and specific biologic processes are associated with the development of nodal metastasis. Such profiles can be exploited for the improved prediction of outcome, selection for adjuvant treatment and development of targeted therapies.

Table 1

Name of Gene	Fold Increase	Category
HIP1	1.3	Apoptosis Inhibitor
NEK7	1.3	Apoptosis Inhibitor
RIT1	1.4	Dedifferentiation
MPGES	1.4	Dedifferentiation
EIF5A2	1.4	Invasion
RUNX2	1.5	Invasion
OXR1	1.5	Immunomodulation
IL7	1.5	Immunomodulation

P79

Is survival reduced for patients with anal cancer requiring surgery after failure of radiation? R.P. Kiran,* N. Pokala, V.W. Fazio. *Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, OH.*

Introduction: Radiation combined with chemotherapy is the primary treatment of anal cancer. Surgery is reserved for failure of combination therapy but there is little data examining outcomes for this group of patients. From a prospective population-based database with data on radiation and surgical therapy, we compare outcomes for anal cancer patients undergoing surgery after radiation(SRT) with patients undergoing radiation alone(RT). Methods: Patients undergoing surgery after radiation for cancer of the anus, anal canal and cloacogenic zone from 1983-2002 were identified from the SEER database. Those with distant disease, sarcoma, lymphoma, overlapping lesions of the rectum/anal canal and those undergoing only local therapy and excisional biopsy were excluded. Patient and tumor characteristics of SRT and RT were compared using Chi-squared, Fisher's exact and ANOVA tests. Kaplan-Meier and logrank

tests were used to determine survival and significance of difference between groups. P<0.05 was considered significant. Results: After the above exclusions, patients with surgical codes for abdominoperineal resection, resection of primary site with/without lymph node dissection and radical resection of adjoining organs were included under SRT. There were 957 RT and 235 SRT patients. RT and SRT had similar median age(62 vs 60 years, p=0.2), gender(male: 34.9 vs 37.4%, p=0.5), site of tumor(anal canal: 46.4 vs 47.7%, p=0.1) and type of radiation(external beam: 95.8 vs 95.3%). SRT had more poorly differentiated and anaplastic tumors(p<0.0001) with regional disease(60.9 vs 42.9%, p<0.001) when compared with RT. Median survival for SRT was however similar to RT(85 vs 89 months, p=0.9). Conclusion: For tumors of the anus, anal canal and cloacogenic region, patients with poorly differentiated and anaplastic tumors with regional disease are more likely to require surgical resection after radiotherapy. Median survival for such patients is comparable to that of patients undergoing radiation alone. Since radiation is usually administered in combination with chemotherapy, this suggests that salvage surgery following failure of initial therapy results in favorable outcomes.

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Prognostic Relevance of *Tensin4* Expression in Human Gastric Cancer K. Sakashita,[1]* K. Mimori,[1] F. Tanaka,[1] Y. Kamohara,[1] H. Inoue,[1] K. Hirakawa,[2] M. Mori.[1] *1. Surgery, Medical Institute of Bioregulation, Kyushu University, Beppu, Japan; 2. Osaka City University Graduate School of Medicine, Osaka, Japan.*

Introduction: *Human Tensin4* (*TNS4*) gene, which belongs to *Tensin* gene, has involved in various biological events by mediating signal transduction. It shows an alterative expression in various types of malignancies. The purpose of this study is to clarify the clinical and pathological significances of *TNS4* expression in gastric cancer. Method: A total of 114 gastric cancer patients who underwent surgical resection were enrolled in this study, and paired samples obtained from tumor tissue and the matched normal mucosa were prepared. Total RNA was extracted, and then the expression level of *TNS4* mRNA was quantified using real-time quantitative reverse transcription-PCR (RT-PCR) method. In addition, the relationship between clinicopathologic factors and *TNS4* expression status was statistically analyzed. Results: The expression level of *TNS4* in tumor tissue was significantly higher than that in normal tissue (p<0.0001). The 114 cases were divided into two groups by the median of *TNS4* expression level in tumor tissue. The cases with higher *TNS4* expression tumor showed histologically poorer grade (p<0.02), deeper invasion to the muscular layer (p<0.05) or serosal layer (p<0.01), more positive lymph node metastasis (p<0.02) or peritoneal dissemination (p<0.05), and higher cancer related death (p<0.05). Furthermore, a Kaplan-Meier curve demonstrated that the patients with higher *TNS4* expression tumor showed significantly poorer prognosis (p<0.01) than those with lower *TNS4* expression tumor (the 5-year overall survival rate was 40.7% and 59.7%, respectively). Especially, the 2-year overall survival rate was 48.2% and 83.1%, respectively, and was very significantly different. Moreover, a multivariate analysis revealed that *TNS4* expression status was an independent prognostic predictor (relative risk: 1.46, 95% confidence interval; 1.05-2.08, p=0.02). Conclusions: *TNS4* gene was overexpressed in gastric cancer tissue, and the tumors with *TNS4* higher expression showed biologically aggressive behavior. The study clarified that *TNS4* expression status is a novel independent prognostic predictor.

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Omentoplasty in rectal cancer surgery prolonges postoperative ileus I. De Hingh,* Y. Klaver, S. Nienhuis, G. Niewenhuijzen, H. Rutten. *Surgery, Catharina Ziekenhuis Eindhoven, Eindhoven, Netherlands.*

Introduction: Omentoplasty is frequently used in rectal cancer surgery for wrapping of the anastomosis or filling up the pelvic cavity. Although there is no consensus in effectiveness of this safeguard, the omentum is known for its infection defence, and haemostatic and angiogenic properties. Disadvantages are additional operating time and the risk of complications. One complication was hypothesised to be prolonged postoperative ileus, as omentoplasty interrupts the blood flow from one of the epiploic arteries to the stomach. Methods: All consecutive patients treated for primary rectal cancer in our hospital between January 2006 and March 2007 and without complications interfering with postoperative bowel functioning were included. Clinical parameters of postoperative ileus were collected and compared between procedures with a concomitant omentoplasty (n=31) and without (n=20). Results: Patients who had a concomitant omentoplasty needed their gastric tube significantly longer than those without (3.9 versus 1.6 days, p<.001). Similar significant disadvantageous results in case of an concomitant omentoplasty were found for time to normal diet (p=.004), time to first discharge of feces (p=.007), need for parenteral feeding (p=.036) and length of hospital stay (p=.008). Furthermore, there was a nonsignificant trend for more days to first discharge of air (3.4 versus 2.4 days, p=.165). There were no significant differences in patients' and procedure characteristics, except for more low anterior resections in the group without an omentoplasty (p<.001). None of these characteristics did clinically relevant interfere with the parameters of postoperative ileus. Discussion: A trend for prolonged postoperative ileus was found in patients who underwent an omentoplasty concomitant with their treatment of primary rectal cancer. When assessing the importance of omentoplasty in the future, the risk of a prolonged postoperative ileus should be taken into account.

P82

Intensive Follow-Up after Curative Surgery for Colon Cancer T. Higuchi,* K. Sugihara. *Surgical Oncology, Tokyo Medical and Dental University Graduate School, Tokyo, Japan.*

Introduction: The patients who underwent curative surgery for colon cancer are regularly followed up. Identification of recurrent tumors which fit for surgical resection improves the prognosis. The aim of this study is to evaluate risk factors of recurrence after curative surgery for colon cancer and to investigate an optimal follow-up system after curative surgery. Patients and Methods: The consecutive 3804 patients with colon cancer, who underwent curative resection at 16 institutions in Japan of the Study Group on Postoperative Follow-Up of Colorectal Cancer Patients from January 1991 to December 1996, were enrolled in this study. A common follow-up system consisted of carcinoembryonic antigen measurement every 3 months, ultrasonic imaging for liver every 3-6 months, chest X-ray every 6 months and colonoscopy every 1-2 years. When recurrences were suspected, CT or/ and MRI were applied. The median follow-up period was 83 months. The 5-year overall survival was 83.1%. Recurrence time, rate, and site, risk factors of recurrence, treatments for recurrent tumors and outcome of re-resection were investigated. Results: The recurrences were observed in 13.3% for right colon cancer, and 16.7% for left colon cancer. Recurrences were found 7.3% in liver, 3.5% in lung, 2.9% in local, 1.5% in peritoneum, and 0.9% in the other organs. 78.7% and 90.5% of recurrence were found within 3 and 5 years after surgery, respectively. The overall 5-year survival rates of patients with surgery for recurrent tumors were better than those without surgery in each recurrence site; 38.6% vs 6.2% in liver, 43.2% vs 3.0% in lung, 26.1% vs 11.4% in local recurrence. Multivariate analysis disclosed that the following factors in each stage were significantly associated with recurrence: male gender for T2N0, distal colon for T4N any, and retrieved lymph nodes more than 12 for T3/T4N any. Conclusions: Intensive follow-up made a contribution to high rates of re-resections in patients with recurrence after curative surgery for colon cancer. Further trials are required to evaluate the cost effectiveness of intensive follow-up and the efficacy of surveillance methods.

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Upstaging due to sentinel lymph node procedure in colon cancer – a prospective, multicenter study C.T. Viehl,[1]* U. Guller,[1] R. Cecini,[2] I. Langer,[1] A. Ochsner,[3] L. Terracciano,[4] H.M. Riehle,[5] U. Laffer,[2] D. Oertli,[1] M. Zuber.[3] *1. Department of Surgery, University of Basel, Basel, Switzerland; 2. Department of Surgery, Spitalzentrum Biel, Biel, Switzerland; 3. Department of Surgery, Kantonsspital Olten, Olten, Switzerland; 4. Institute of Pathology, University of Basel, Basel, Switzerland; 5. Viollier Histopathology/Cytology, Basel, Switzerland.*

Introduction: The value of sentinel lymph node (SLN) procedure in colon cancer patients remains a matter of great debate. Therefore, the objective of this large prospective, multicenter trial was threefold: first, to evaluate the identification rate and accuracy of the SLN procedure for colon cancer patients; second, to analyze factors influencing the identification rate; and third, to assess the extent of upstaging due to the SLN procedure. Methods: One hundred ninety-two patients with biopsy proven colon cancer (stage I: n=32, stage II: n=78, stage III: n=64, stage IV: n=18) underwent open, oncologic colon resection. SLN procedure was performed in vivo according to a standardized protocol: isosulfan 1% was injected around the tumor, blue staining lymph nodes were tagged and processed separately. Three levels of each SLN were stained with H&E and immunohistochemistry (IHC) with the pancytokeratin marker

AE1/AE3. Percentages were compared using the chi-square test. Results: SLN identification was successful in 164/192 patients (identification rate 85.4%). The accuracy of the procedure was 83.5%, sensitivity 57.1%, specificity 100.0%, and negative predictive value 78.9%. Successful SLN identification depended on the intraoperative identification of blue stained lymphatic vessels (p<.001). Median number of sampled SLN was 3 (range 1-20), and median number of Non-SLN was 20 (range 1-57). SLN were significantly more likely to contain tumor infiltrates than Non-SLN (p<.001). Due to the use of IHC in identified SLN, small nodal tumor infiltrates were found in 16 of 104 stage I and II patients considered node-negative in initial H&E analysis, thus resulting in upstaging of 15.4% of these patients. Conclusions: The sentinel lymph node procedure for colon cancer has good identification and accuracy rates. Blue stained lymphatic vessels facilitate identification of SLN. Most importantly, the SLN procedure results in upstaging of over 15% of stage I and II patients. The potential advantage of performing the SLN procedure appears to be particularly important in these patients as they may benefit from adjuvant chemotherapy.

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Infra-levator lymphatic drainage of low rectal cancers as a ground for the abdominosacral resection (ASR) M. Bebenek.* *Regional Comprehensive Cancer Center, Wroclaw, Poland.*

INTRODUCTION Some low-rectal cancers may spread into or recur in the inguinal lymph nodes despite the optimal resection of the primary tumor. Hence, we hypothesized that the lymphatic drainage of low-rectal adenocarcinomas may be inhomogeneous and that an extra-mesorectal route may be involved in at least some cases. The idea of our preliminary study was to analyze potential lymphatic drainages in low-rectal cancer patients. METHODS The clinical records of 206 consecutive low-rectal cancer patients operated on between May 5, 1998 and June 30, 2006 were analyzed for the presence of metachronous or synchronous inguinal lymph node metastases. Moreover, the lymphatic drainage of the primary tumor was traced with Patentbalu V dye injected into the tumor of two consecutive low-rectal adenocarcinoma patients who were free from inguinal lymph node metastases. RESULTS An analysis of consecutive 206 low-rectal cancer patients revealed six cases of metachronous or synchronous inguinal node metastases. The median age of patients was 55 years. They were all diagnosed with rectal adenocarcinoma, T3 or T4 tumors located in the lower one third of the rectum. An evaluation of Patentblau-stained surgical specimens from two consecutive rectal cancer patients revealed extramesorectal lymphatic drainage of the primary tumor besides the mesorectal route. The lymphatic vessels that left the primary tumor formed numerous anastomoses in the rectal wall. Some of them drained directly to the lymphatic system of the infralevator compartment. Primary tumors in these two cases analyzed were located 2 cm and 5 cm from the anal verge, respectively. CONCLUSIONS The demonstration of an alternative route of lymphatic drainage suggests that more radical surgical procedures like ASR, including the infralevator compartment resection, are essential for the successful treatment of low-rectal cancers.

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Role of surgical resection in patients with metastatic pancreatic adenocarcinoma K. Vanderveen,[1]* S.L. Chen,[1] R. Canter,[1] D. Yin,[2] R.D. Cress,[2] R.J. Bold.[1] *1. Surgery, University of California - Davis, Sacramento, CA; 2. California Cancer Registry, Sacramento, CA.*

Background: Considerable controversy surrounds a possible survival advantage for patients with metastatic breast cancer who undergo removal of the primary tumor. Limited data exists for other metastatic solid tumors, particularly pancreatic adenocarcinoma (PaCa), which has a more rapid pace of disease. Utilizing a population-based dataset, we sought to analyze the impact of surgical resection on survival in patients with known metastatic PaCa. Methods: Through the California Cancer Registry, we identified patients diagnosed with PaCa between 1994 and 2002. The study population included all patients diagnosed at presentation with metastatic disease. Factors potentially impacting survival were analyzed, including: age, gender, tumor characteristics, lymph node status, receipt of systemic therapy, and surgical resection. Univariate survival analysis was performed by the Kaplan-Meier method. Multivariate analysis was performed by Cox regression. Results: Median overall survival of the 11,663 patients diagnosed with metastatic disease at presentation was 3 months. Of these, 253 (2%) underwent resection of the primary tumor as the initial component of their treatment. Resected patients were slightly younger (mean age 61 vs. 68 yrs, p<0.001), but otherwise similar in gender distribution (51% vs. 50% male) and receipt of chemotherapy and/or radiation (57% vs, 56%). Median survival was longer for resected vs. unresected patients (7 mo. vs. 3 mo., p<0.001); one-year survival was 36% in resected vs. 8% in unresected patients. However, on multivariate analysis, after adjusting for patient demographics, tumor characteristics, and receipt of systemic therapy, surgical resection was not associated with any significant improvement in survival. Conclusions: Unlike other disease sites with a more indolent pace of disease, surgical resection of the primary tumor is not independently associated with improved survival in patients with metastatic PaCa. The observed improvement in survival in those undergoing resection may reflect selection bias of a very small fraction of patients with favorable variables including younger age, better health status, and limited extent of disease.

P86

The Twelve Lymph Node Standard in Colon Cancer: Can it be Achieved? G.J. Chang,* S.H. Taylor, M.A. Rodriguez-Bigas, J.M. Skibber. *Surgical Oncology, U.T. M.D. Anderson Cancer Center, Houston, TX.*

INTRODUCTION: A minimum standard of 12 lymph nodes (LN) examined during curative resection of colon cancer has been proposed. The purpose of this study was to evaluate the feasibility of a 12 LN standard during colon cancer resection using single institution tumor registry data and to evaluate variability in the process of LN recovery. METHODS: Consecutive cases of non-metastatic colon cancer surgically treated from 1998-2005 were identified from the institutional tumor registry. Patient, tumor, and pathologic variables were evaluated. No LN revealing procedures were utilized. A statistical process control chart was used to examine variation and outliers during lymph node examination. RESULTS: 480 patients were identified. Median age was 62.5 years (interquartile range [IQR] 50-75). Sex was male in 53% and female in 47%. Tumors were right-sided in 45% and left-sided in 43% and AJCC stage I in 22.5%, II in 37.9% and III in 39.6%. The median number of LN examined was 18 (IQR 13-26) overall and increased from 14 (IQR 11-27) in 1998 to 22 (IQR 17-33) in 2005. The proportion with ≥12 LN increased from 62.3% in 1998 to 94.3% in 2005 (P<.00001, Armitage, table) and corresponded to an increased multidisciplinary emphasis on adequate lymph node evaluation. Control chart analysis demonstrated the LN examination process demonstrated little process variability and outliers were primarily attributable to high LN numbers. However tumors located in the transverse or left colon were more likely to be associated with the recovery of <12 LN than tumors on the right (P=.0003, chi-square). CONCLUSIONS: The process of LN examination during colon cancer resection can be improved and examination of at least 12 can be achieved in nearly every case. However the total number of lymph nodes recovered may be influenced by non-technical factors such as tumor location.

Percent of cases by # LN examined

YEAR	<12 LN	12-17 LN	18-25 LN	>25 LN
1998	37.7	31.1	14.8	16.4
1999	32.7	28.6	22.4	16.3
2000	26.8	35.7	16.1	21.4
2001	26.8	25	28.6	19.6
2002	23.8	30.2	19.0	27.0
2003	13.0	17.4	34.8	34.8
2004	6.5	24.2	30.6	38.7
2005	5.7	21.8	35.6	36.8

P87

Peripheral blood gene profiling independently predicts outcome of patients with gastric cancer S. Mocellin, S. Gobbo, L. Bertazza, A. Marchet,* D. Nitti. *oncological & surgical sciences, university of padova, Padova, Italy.*

Introduction: Although the AJCC TNM staging system is the most widely used prognostic tool to identify large subgroups of patients with significantly different clinical outcome, its prognostic power is modest on a single patient basis. We tested the hypothesis that the gene expression profiling of peripheral blood might predict the survival of patients with gastric cancer independently of the TNM system. Methods: Fifty one patients affected with stage I to IV gastric cancer were prospec-

tively enrolled in this study. Preoperatively, a single peripheral blood sample (10 ml) was withdrawn from each patient. Using quantitative real time PCR, the following cancer related genes were analyzed: cytokeratin-19, CEA, survivin, VEGF, CD133, and PRAME. Using the Cox proportional hazards model, patients' overall survival was correlated with the following predictors: sex, age, TNM stage, and the mRNA levels of the above mentioned genes. Results: The transcriptional levels of the considered cancer related genes resulted higher in patients rather than in healthy controls with the following rates: cytokeratin-19: 50%, CEA: 57%, survivin: 98%, VEGF: 43%, CD133: 25%, PRAME: 10%. The expression of no single gene significantly correlated with patients' TNM stage. At univariate survival analysis, only TNM stage significantly correlated with patients' overall survival. Interestingly, at multivariate analysis (stepwise variable selection mode) the only variables retained by the Cox model (likelihood score P=0.018) were CEA (P=0.0001), survivin (P=0.0001) and VEGF (P=0.043). Conclusions: We identified a peripheral blood gene expression profile that independently correlates with the survival of patients with gastric cancer. This gene signature might reflect the presence of circulating tumor cells, cancer stem cells, and / or endothelial progenitor cells playing a pathogenetic role in the metastatic process of gastric cancer. If validated in larger series, these findings might provide clinicians with a valuable, easy-to-obtain tool for the personalized treatment of gastric cancer, such as the selection of patients who most benefit from adjuvant regimens.

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Incidence and Impact of Lymph Node and Non-Peritoneal Metastases in Non-Carcinoid Epithelial Tumors of the Appendix
M.H. Katz,[1]* P.F. Mansfield,[1] R.A. Wolff,[1] C. Eng,[1] C. Ng,[1] S. Gonzalez-Moreno,[2] L.A. Lambert.[1] *1. The University of Texas, MD Anderson Cancer Center, Houston, TX; 2. Centro Oncologico MD Anderson International Espana, Madrid, Spain.*

INTRODUCTION: Aggressive histopathology and non-peritoneal metastases (NPM) are considered relative contraindications to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with non-carcinoid epithelial tumors of the appendix (NCETA). However little is known about the true incidence and impact of lymph node (LN) metastases and NPM in patients with these tumors. METHODS: Medical records of all patients who presented to a single institution with a diagnosis of NCETA between February 1992 and August 2007 were retrospectively analyzed. Data regarding primary tumor histology (Grade 1: low grade or well-differentiated; Grade 2: moderately differentiated; Grade 3: poorly differentiated or signet ring cell), regional LN status (when mesenteric dissection was performed), presence of NPM, therapeutic strategy, and survival from the time of diagnosis were assessed. RESULTS: 270 patients with NCETA were identified. 153 (57%) patients had grade 1 tumors, 23 (8%) grade 2 and 94 (35%) grade 3. LN status was available for 160 (60%) patients, of whom 52 (33%) had lymph node metastases (Table). NPM were identified in 16 (6%) of patients (Table). LN metastases were present in 8 of 9 (88%) patients with both NPM and evaluable LNs. All four patients with grade 1 primary tumors and NPM underwent metastasectomy as part of their surgical management. Median survival after metastatectomy in these patients was 46 months (range 7.5 to 165 months) and all were alive at last follow-up. In contrast, 11 of 12 patients (92%) with NPM and either grade 2 or 3 primaries were deceased at a median follow-up of 8 months after diagnosis of NPM. CONCLUSION: Lymph node metastases occur in 1/3 of patients with non-carcinoid epithelial tumors of the appendix, and are associated with high pathologic grade. Non-peritoneal metastases are uncommon, even in patients with high grade tumors and lymph node metastases; therapies should be developed with this in mind. Aggressive surgical therapy may be beneficial in select patients with low-grade disease and non-peritoneal metastases.

Histopathology in 270 patients with non-carcinoid epithelial tumors of the appendix.

Grade	N	Node Data n (%)	Positive Nodes n (%)	p	NPM n (%)	p
1	153	81 (53)	4 (5)		4 (3)	
2	23	20 (87)	6 (30)	< 0.005	2 (9)	< 0.05
3	94	59 (63)	42 (71)		10 (11)	
Total	270	160 (60)	52 (33)		16 (6)	

Node Data = patients for whom node status was available. NPM: Non-peritoneal metastasis

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Phase II study of oxaliplatin, UFT and leucovorin in patients with surgically non-curable or metastatic gastric cancer in out-patient setting
A.F. Drenth,[1]* E.J. Siemerink,[2] J.T. Plukker,[1] W.J. Sluiter,[2] N.H. Mulder,[2] G.A. Hospers.[2] *1. Dept Surgical Oncology, University Medical Center Groningen, Groningen, Groningen, Netherlands; 2. Dept of Medical Oncology, University Medical Center Groningen, Groningen, Groningen, Netherlands.*

Introduction: Many combination chemotherapies have been explored for patients with incurable gastric cancer. Some of them, including the common used ECF regime showed high response rates (20-40%) with modest survival benefits at the cost of relatively high toxicity and the need for hospitalisation. In a phase II study of oxaliplatin, uracil plus tegafur (UFT) and leucovorin we report the toxicity and anti-tumor activity of this regimen an out-patient setting. Methods: Patients received oxaliplatin 130 mg/m2 on day 1, followed by UFT 350 mg/m2 and leucovorin 90 mg from day 1-14, and no study medication from day 14-21, for a maximum of 6 cycles. The primary endpoint was response rate. Secondary endpoints were survival and toxicity according to NCI-CTC. Results: Twenty patients were included: 19 men and 1 woman; median age 60 years; WHO-PS 0/1/2/ in 12/6/2 patients. Site and rate of the metastases were liver 65%, lymph nodes 65%, bone 20%, lung 15% and other 15%. During the follow-up period of the study 80% of the included patients have died. The overall response rate was 35%, with 1 patient showing a complete clinical remission. The median overall survival was 7.1 month (95% CI 3.5-10.6). The overall clinical reported toxicity consisted of grade 2 neuropathy in 11 pts (55%) grade 2 diarrhoea in 5 pts (25%), grade 3 diarrhoea in 2 pts (in 10%), weight loss in 5 pts (25%). Pulmonary embolism occurred in 2 pts (10%). One of these patients died, this was the only mortality observed within 30 days Conclusion: This out-patient treatment regime of oxaliplatin, UFT en leucovorin is associated with a response rate and overall survival similar to the more intense hospitalisation requiring ECF regime for patients in a palliative setting.

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A Critical Appraisal of the Surgical Management of Gallbladder Cancer in the United States
E.H. Jensen,* A.A. Abraham, E.B. Habermann, W.B. Al-Refaie, B.A. Virnig, T.M. Tuttle. *Surgery, University of Minnesota Medical Center, Minneapolis, MN.*

Radical resection improves survival in selected patients with gallbladder (GB) cancer. Current guidelines recommend radical resection including at least 2cm of GB fossa and portal lymph node dissection as optimal treatment for patients with early stage disease (including T1B-T3). Our aim was to determine compliance with current treatment recommendations for patients with early stage GB cancer. Methods: We performed a population based cohort study using the Surveillance Epidemiology and End Results (SEER) database. Patients with stage 0, I or II gallbladder cancer who underwent surgical resection (simple cholecystectomy or radical resection) were identified from the SEER tumor registry from 1988 to 2004. We excluded patients who did not undergo surgical resection, or with AJCC stage III, IV, or unknown. The proportion of patients undergoing radical resection was determined for each T stage. Results: We identified 4769 patients who underwent surgical resection for early stage GB cancer between 1988 and 2004. A total of 496 (10.4%) patients underwent radical resection while 4273 (89.6%) underwent simple cholecystectomy alone. The proportion of patients who underwent radical resection for T1B, T2, and T3 cancers was 4.6%, 5.6%, and 18%, respectively. We identified a significant trend towards radical resection with higher T-stage tumors (p=<0.0001); however, overall only 12.3% of patients with T1B, T2, and T3 tumors underwent radical surgery. Within this group, 125 (25.7%) patients had positive lymph nodes identified on final pathology. Lymph node involvement was most common with T3 tumors (57%). Patients <70 years of age underwent radical surgery more frequently as compared with patients >70 years (12.59% v. 8.97%, p<0.0001). Non-white patients were more likely to undergo radical resection as compared with whites (12.39% v. 9.94%, p=0.0277). Gender was not significantly associated with rates of radical resection. Conclusion: Despite evidence based guidelines, radical resection for early stage GB cancer appears significantly underutilized. Ensuring the delivery of recommended treatment may improve outcomes for patients with this disease.

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High Volume Centers Improve Long-Term Survival for Patients with Cancers of the Head and Neck E.A. Perez,* M.A. Molina, M.C. Cheung, J.C. Guiterrez, L.G. Koniaris. *Department of Surgery, University of Miami, Miami, FL.*

Objective: To define the prognostic significance of surgical center case volume on outcome for head and neck cancer (HNC). Methods: The Florida Cancer Data System (1998-2005) was queried for surgical patients undergoing resection for HNC. Medical facilities were ranked by HNC operative volume and classified in high, medium and low volume centers. Results: A total of 11,160 patients undergoing surgery for HNC were identified. Low-volume centers (LVCs) treated 31.8% of the patients while 33.9% were treated at medium-volume centers (MVC) and 34.3% at high volume centers (HVC). African American patients (43%) were treated more frequently at HVC while Hispanic patients were treated more often at MVC ($p < 0.001$). A larger proportion of high-grade tumors (45.8%) and lesions over 30mm (43.2%) were resected at HVC ($P < 0.001$). Superior median survival time was observed for the cohort treated at HVC when compared to those treated at MVC or LVC (59 months vs. 52 months vs. 47 months respectively, $p < 0.0001$). Additional treatment modalities such as radiation and chemotherapy were more frequently administered at HVC. By univariate analysis, improved survival was observed for tumors located parotid, larynx and pharynx when treated at a HVC. Superior survival was observed at HVC for tumors of grades I, II and III and all sizes. Multivariate analysis identified treatment at a HVC as a significant independent predictor of improved survival (HR = 1.241, P = 0.005). Conclusions: Surgical treatment for HNC at HVC results in significantly improved long-term survival. 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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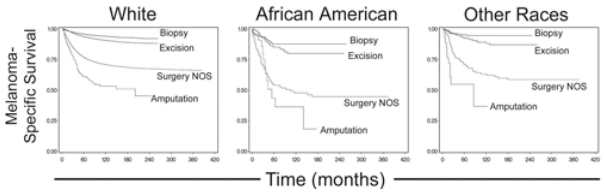
Race Differences in Survival After Surgical Treatment for Melanoma R.C. Fields,* K. Collins, Y. Liu, D.B. Jeffe, J.F. Moley. *Department of Surgery (RCF, JFM); Division of Health Behavior Research, Department of Medicine (KC, YL, DBJ); and Siteman Cancer Center, Washington University School of Medicine, Saint Louis, MO.*

INTRODUCTION: Melanoma is relatively uncommon in African Americans and outcomes after surgical treatment are poorly characterized. Small series indicate that melanoma presentation and outcomes may differ by race or ethnicity; however, these studies have been limited by a low incidence of disease in non-Whites and have not compared survival across racial and ethnic lines with respect to surgical treatment of melanoma. **METHODS:** We analyzed data from the 1973 - 2004 Surveillance, Epidemiology and End Results (SEER) Program using Cox proportional hazard models to compare the effects of surgical treatment on overall and melanoma-specific survival in African Americans, Other races, and Whites, controlling for confounding demographic and tumor-related variables. **RESULTS:** We identified 151,204 patients with first primary melanoma (148,883 Whites, 789 African Americans and 1,532 Other races. The 10-year melanoma-specific survival was lower in African Americans (73%), than in Whites (88%) and Other races (85%). Melanoma-specific survival was poorer for African Americans regardless of type of surgery (Figure). In multivariable analysis, receipt of surgical treatment (compared with no surgery) was associated with lower likelihood of melanoma-specific mortality among Whites (HR = 0.38, CI = 0.36 - 0.41, $p < 0.0001$), and Other races (HR = 0.30, CI = 0.17 - 0.51, $p < 0.0001$), but not among African Americans (HR = 0.63, CI = 0.32 - 1.25, $p = 0.1844$). An overall survival advantage held true for Whites and Other races as well. **CONCLUSIONS:** Overall and melanoma-specific survival was lower in African Americans undergoing surgical treatment for melanoma than in Whites and Other races. In contrast to outcomes for Whites and Other races, undergoing surgical treatment was not an independent predictor of survival for African Americans with melanoma. The reasons for these disparities are poorly understood.



Kaplan-Meier curves of melanoma-specific survival among Whites, African Americans, and Other Races after surgical treatment for primary melanoma. NOS = not otherwise specified.

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Association of Increased Number of Sentinel Lymph Nodes with Unfavorable Pathologic Features of Primary Melanoma C.R. Schmidt,[1]* K.S. Panageas,[2] D. Coit,[1] A. Patel,[1] M.S. Brady.[1] *1. Department of Surgery, Gastric and Mixed Tumor Service, Memorial Sloan-Kettering Cancer Center, New York, NY; 2. Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY.*

INTRODUCTION: The pathologic status of the sentinel lymph node (SLN) is the most powerful prognostic factor for patients with intermediate thickness melanoma. We have previously demonstrated that lymphatic drainage to more than one regional node basin is independently associated with poor outcome in patients with truncal melanoma. We hypothesize that increased peritumoral lymphatics also increase the number of SLNs identified and this may be associated with poor outcome. METHODS: We evaluated the impact of number of SLNs removed in 970 patients undergoing SLN mapping for cutaneous melanoma at our institution between 1996 and 2006. Patients with multiple primaries (n=144), no SLN identified (n=1) or clinical stage > IIC (n=37) were excluded. We evaluated factors associated with the number of SLNs removed using multivariate Poisson regression and determined whether an increased number of SLNs was associated with poorer overall (OS) or recurrence-free survival (RFS). All blue stained and radioactive lymph nodes after intradermal injection of 1% Lymphazurin blue dye and technetium-99m-sulfur colloid were included in the total SLN count. RESULTS: The median follow-up was 36 months. The median number of SLNs removed was 2.0 (range 1-20 nodes). Clinical factors independently associated with increased number of SLNs were younger age (P=0.017) and head and neck primary site (P<0.001). Pathologic factors associated with an increased number of SLNs were lymphovascular invasion (LVI) (P=0.002) and increased Breslow thickness (P=0.004). There was no association between number of SLNs removed and OS or RFS in all 970 patients or in the subgroup of patients with negative SLNs (n=803). DISCUSSION: An increased number of SLNs is associated with poor pathologic features of the primary melanoma, specifically LVI and increased Breslow depth. An increased number of SLNs is also associated with head and neck site and younger age. Although the number of SLNs is not an independent prognostic factor, drainage to multiple SLNs is more common in the setting of an increased Breslow depth and LVI, suggesting that these adverse factors enhance peritumoral lymphangiogenesis.

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The Significance of Multiple Metastatic Foci in Sentinel Lymph Nodes of Melanoma R.L. Neff,* O. Al-Saif, S. Sharif, C. Bozek, D.A. Agnese, L.A. DeRenne, S.P. Povoski, M.J. Walker. *Surgical Oncology, Ohio State University, Columbus, OH.*

Introduction- Since the introduction of sentinel lymph node (SLN) biopsy, controversy has surrounded its utility and prognostic value. Quantification of the extent of metastatic disease in the SLN has been used to tailor local therapy in breast cancer. The significance of micrometastatic disease in melanoma is unknown and addressed in this study. Methods- An IRB approved prospective melanoma sentinel lymph node database with

over 1200 patients (pts) was searched for positive sentinel nodes. Of 206 pts identified, 64 (31%) to date had their SLN slides re-reviewed by one pathologist(LD) and characterized by the size and number of metastatic foci. These 64 patients form the basis of this report. Results- Twenty-six patients with multiple metastatic foci in the SLN were compared to 38 patients with a single metastasis. All patients underwent completion lymphadenectomy with a median survival of 5.83 years. The median size of metastasis was 2.0 mm (range, 0.06 to 27). On univariate anlaysis, there were no significant differences with regard to age, gender, number of SLN harvested, primary tumor depth, ulceration, lymphovascular invasion, or mitoses >1/hpf for the two groups. Multiple foci of metastasis was associated with the finding of additional metastatic nodes within the completion lymphadenectomy specimen, and subsequent higher rate of locoregional recurrence (Table 1). Conclusion- The management of the regional lymph nodes in the era of SLN in melanoma remains somewhat controversial. The presence of multiple metastatic foci in SLN is a predictor of poor prognosis and supports the consideration for further adjuvant therapy in the setting of clinical trials.

Table 1. Characteristics of single vs. multiple metastatic foci in SLN of melanoma patients

		Single Foci	Multiple Foci	p-value
Patients		38	26	
Age (mean)		57.16	53.27	0.339
Male/ Female		20/18	15/11	0.800
Primary	Mean Depth (mm)	3.74	3.34	0.564
	Ulceration	13	7	0.593
	LVN invasion	7	9	0.156
	Mitoses >1/hpf	15	13	0.450
# SLN (mean)		3.03	3.23	0.775
# (+)SLN		1.32	1.81	0.201
(+) Completion LND		6	11	0.024
Recurrence	Locoregional	5	9	0.064
	Distant	9	4	0.534

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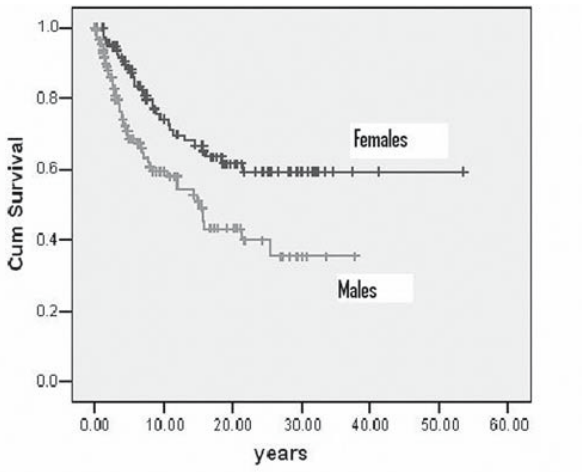
Do Sex Related Survival Differences in Cutaneous Melanoma Apply to the Pediatric Population? S.H. Telian,* A.M. Terando, M.B. Faries, R. Essner, D.L. Morton. *John Wayne Cancer Institute, Santa Monica, CA.*

Introduction: The incidence of melanoma in children is rapidly increasing. Female sex carries a significant survival advantage in the adult population, but its significance among pediatric patients is less clear, possibly because reported studies have been too small or too heterogeneous to identify prognostic impact. Methods: Our institution's prospective melanoma database of >13,000 records was queried to identify patients diagnosed with cutaneous malignant melanoma up to 19 years of age. Variables included sex, location and Breslow depth of the primary melanoma, and stage at presentation. Kaplan-Meier and log rank were used to estimate and compare survival data. Results: Of the 239 patients identified, 120 (50.2%) were female. Mean age was 16.25 years (range, one week to 19 years). Females had a significantly increased overall survival as compared with males (Figure). 5-year survival rates were 68.6% and 88.2% for males and females, respectively (p=0.002). Breslow depth and head/neck or truncal primary site were significant adverse prognostic indicators (p=0.001 and p=0.018, respectively). AJCC stage groupings maintained their prognostic implications for the pediatric population (p<0.001). Conclusions: We report the largest single-institution series of patients with pediatric melanoma. Our results confirm that as reported within the adult population, female sex confers a survival benefit in pediatric patients with cutaneous melanoma. As expected, Breslow depth, location of primary and stage at diagnosis are also important prognostic variables for pediatric patients.



Overall survival in pediatric patients by gender.

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FDG-PET and CT in the staging of melanoma patients with lymph node metastases; diagnostic performance and clinical consequences E. Bastiaannet,[1]* T. Wobbes,[2] O.S. Hoekstra,[3] A.H. Brouwers,[1] W.J. Oyen,[2] S. Meijer,[3] H.J. Hoekstra.[1] *1. University Medical Centre Groningen, Groningen, Netherlands; 2. University Medical Centre Nijmegen, Nijmegen, Netherlands; 3. VU University Medical Centre, Amsterdam, Netherlands.*

Introduction. Accurate staging of melanoma patients with palpable lymph node metastases (AJCC stage III) is essential to determine appropriate (surgical) treatment. A prospective, multicenter study was performed to investigate the value of 18F-fluorodeoxy-glucose (FDG) Positron Emission Tomography (PET) and spiral Computed Tomography (CT) in the staging of melanoma patients stage III and to assess the clinical consequences. Methods. Whole-body FDG-PET and spiral CT imaging was performed in patients with palpable, histology/cytology proven lymph node metastases. Patients were considered "upstaged" if distant metastases were depicted on PET or CT (stage IV disease). Either pathological confirmation or at least 6 months follow-up served as standards of reference for evaluation of the diagnostic performance. Intended and performed treatment was compared to define a change in treatment as result of the two scans. Results. From March 2003 until February 2007, 207 patients,128 males (62%) and 79 females (38%) with a median age of 57.9 (range 23.2-86.8) years were included. Lymph node metastases were in the neck 20.7% (n=43), axilla 33.2% (n=69) and groin 46.2% (n=95). Upstaging with PET was 29.6% (n=61), in 85.3% (n=52) True-Positive (TP). Upstaging with spiral CT was 27.7% (n=57), in 80.7% (n=46) True-Positive (TP). Overall percentage of "true-upstaging" with PET was 25.2% and CT 22.3% (p=0.18). PET detected more metastatic sites than CT (p=0.049). Treatment changed in 38 patients (18.4%); in 27 patients (71.1%) from surgery to palliative chemotherapy and in 11 patients (28.9%) less radical surgery was performed. Conclusions. Overall, 25% of the patients were upstaged. PET is equivalent to spiral CT in upstaging, however PET detected more metastatic sites. PET scan is indicated in the staging of melanoma patients with palpable lymph node metastases, with the CT scan as a good alternative since surgical treatment was cancelled in 13% of the patients and less radical surgery was performed in 5%.

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Management of Melanoma In Situ with Staged Marginal and Subsequent Central Tumor Excision M.G. Möller,[1]* E. Pappas,[2] J.S. Zager,[3] A. Prakash,[1] L.A. Santiago,[2] A. Kinal,[2] C.A. Puleo,[3] F. Glass,[3] J.L. Messina,[2] V.K. Sondak,[3] C.W. Cruse.[3] *1. Surgical Oncology, H. Lee Moffitt Cancer and Resarch Institute, Tampa, FL; 2. University of South Florida College of Medicine, Tampa, FL; 3. Department of Multidisciplinary cutaneous oncology Moffitt Cancer Center, Tampa, FL.*

Introduction: Melanoma in situ (MIS) represents 45% of all melanomas. The margins of MIS are often poorly defined with extensive subclinical disease. Standard fusiform excision with 5 mm margins results in positive margins in up to a third of cases. To decrease the incidence of involved margins, we employ a staged excisional approach for MIS. Initially patients (pts) undergo excision under local anesthesia of a 2-3 mm rim of tissue optimally 5 mm beyond the visible extent of the lesion. This tissue is evaluated by permanent pathology. Any positive margins are further excised. When all margins are negative the central area is then excised and reconstructed. Methods: 43 pts with MIS underwent this procedure from 2004-2007. Demographics, tumor characteristics, margin status, number of re-excisions, type of reconstruction and recurrences were evaluated. Results: 43 pts, 24M: 19F, ages 42-88y (median 71), underwent staged marginal excision prior to definitive central tumor excision and reconstruction. Most tumors were on the head or neck. The surgical defect size ranged from 2-56 cm2 (median 18+15 cm2). Eight pts (18%) required re-excision of at least one margin. Invasive melanoma was found in the final specimen in 6 pts (14%). Surgical defects were reconstructed with flaps in 17 (39%), full-thickness grafts in 18 (41%) and split-thickness grafts in 8 pts (18%). The median time from initial margin excision to completion of excision/repair was 10 days. There have been no local recurrences to date (median follow-up 5.3 months, range 2-18). Conclusions: This technique allows for careful margin analysis and subsequent central tumor excision with simultaneous reconstruction. This approach minimizes the need for a second major operation, which would have been necessary in 18% of our pts if treated by a one-stage approach. It is noteworthy that 14% of patients had invasive melanoma in the final excision specimen. This reinforces the importance of adequate full thickness biopsies of suspicious pigmented lesions prior to any type of surgical management.

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Does Size and Location of Melanoma SLN Metastases Help Predict Non-SLN Involvement T. Frankel,* K.A. Griffith, S.L. Wong, V.M. Cimmino, A.E. Chang, M.S. Sabel. *Surgical Oncology, University of Michigan, Ann Arbor, MI.*

Introduction: We sought to determine whether the size and location of the metastases within the SLN may help identify which melanoma patients have a low likelihood of harboring additional positive non-sentinel lymph nodes (PNSLN). Methods: A review of our IRB approved melanoma database was undertaken to identify all SLN+ patients since we began prospectively measuring the size of the metastatic lesion within the SLN. Size was recorded as a percentage of the surface area of the node. After excluding patients <18 y.o. age and those with incomplete data, 136 patients were available for analysis. Univariate logistic regression techniques were used to assess potential significant associations. Size of the metastases was considered only for patients with a single positive SLN. Decision tree analysis was used to identify which features best predicted patients at low risk for harboring additional disease. Results: The likelihood of finding PNSLN was significantly associated with primary location on the H&N or lower extremity (p=.01), Breslow depth >4mm (p=.001), presence of angiolymphatic invasion (p<0.0001), satellitosis (p=.004), extranodal extension (p=.0002), 3 or more positive SLN (p=.02) and SLN tumor burden >1% surface area (p=.004). Location of the metastases showed no correlation with a PNSLN. Decision tree analysis incorporating size of the metastatic burden within the SLN along with histologic features of the primary melanoma can identify melanoma patients with a positive SLN who have a very low risk of harboring additional disease with the PNSLN. Conclusion: The current recommendations for patients with SLN metastasis is complete removal of lymph nodes within that nodal basin although 80% of patients will not have residual disease identified. Size of the metastatic burden within the SLN, measured as a percentage of the surface area, along with histopathologic features of the primary melanoma, helps stratify the risk of harboring residual disease in the NSLN, and may allow for selective completion lymphadenectomy.

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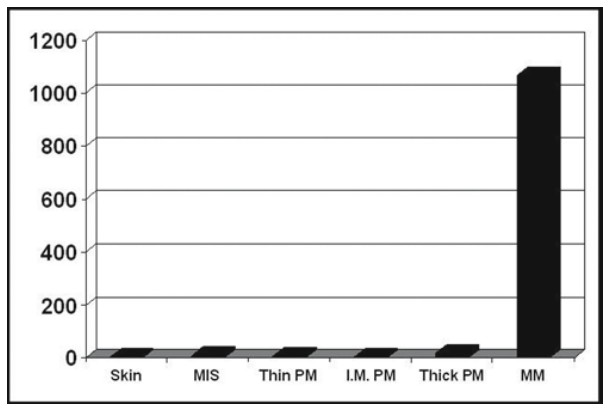
Transcriptional Silencing of the Putative Oncogene, Testis-Specific Protein Y-linked, in Human Melanoma: Implications of Gene Demethylation P.M. Howell,* S. Liu, S. Ren, A.I. Riker. *Surgical Oncology, Mitchell Cancer Institute-University of South Alabama, Mobile, AL.*

Introduction: The testis-specific protein Y-linked (TSPY) gene is described as a putative oncogene in various tumors, involved with enhanced neoplastic cell proliferation. Others have shown TSPY as a tumor suppressor gene (TSG), with aberrant promoter hypermethylation resulting in gene inactivation. We have identified over-expression of TSPY in metastatic melanoma (MM), hypothesizing a potential role in melanoma progression and metastatic potential. Methods: Primary cutaneous melanoma (PM), MM and daughter cell lines were analyzed for TSPY gene expression by cDNA microarray, semi- and real-time quantitative RT-PCR (qRT-PCR) and Western blot analysis. The demethylating agent 5-aza-2'-deoxycytidine (5-azaC) was used to detect pre-and post-treatment changes in promoter methylation and gene expression, determined by quantitative methylation-specific PCR (Q-MSP) and methylation-specific sequencing (MSS). Results: We identified a distinct transition point for TSPY gene expression at the thick primary/MM interface with the parallel loss of TSPY promoter hypermethylation. qRT-PCR revealed 4/7 (57%) MM cell lines over-expressed TSPY, correlating with protein expression by Western blot. Q-MSP and MSS of TSPY promoter regions revealed a high level of methylation (81%) in human melanocytes, averaging 33% for MM. Treatment with 5-azaC resulted in a significant decrease in promoter methylation for all samples examined and a marked increase in TSPY gene expression for two thick primary samples. One, 46% methylated and positive for TSPY gene expression pre-treatment, exhibited a 35-fold increase in expression post-treatment, while another, 67% methylated and TSPY-negative, exhibited a 140-fold increase. Conclusion: We have identified TSPY as a possible metastasis-promoting gene, strongly induced by 5-azaC treatment. Thus, global hypomethylation may have a dichotomous effect upon gene function of putative TSG's and oncogenes, such as TSPY. Ongoing studies will further elucidate the effect of gene demethylation upon melanoma progression and metastatic potential.



TSPY Gene Expression by cDNA Microarray Analysis of Human Melanoma Samples

P100

Efficiency Of Different Models Predicting Sentinel Node Status In 1,104 Melanoma Patients C.R. Rossi,[1]* S. Pasquali,[1] S. Mocellin,[1] P.L. Pilati,[1] D. Nitti,[1] R.P. Saw,[2] R.A. Scolyer,[2] J.R. Stretch,[2] J.F. Thompson.[2] *1. Department of Oncological and Surgical Sciences, University of Padova, Padova, Italy; 2. Sydney Melanoma Unit, The University Of Sydney, Sydney, NSW, Australia.*

Background Approximately 20% of melanoma patients undergoing sentinel node biopsy (SNB) harbor metastatic disease. With no conclusive evidence of a survival benefit of SNB, about 80% of patients currently submitted to SNB are likely overtreated. We tested the efficiency of different models in predicting the status of sentinel nodes harvested from the largest series ever considered for this purpose. Patients and methods The clinico-pathological records of 1,104 melanoma patients who underwent SNB were analyzed. The following predictive variables were considered: age, sex, Breslow thickness, Clark level, ulceration, regression, mitotic index and histological subtype. Logistic regression, support vector machine, single tree and decisional tree forest models were fitted to the data. The models obtained were validated using a cross validation method, the main aim being to maximize the negative predictive value (NPV) and to minimize the number of patients overtreated. Results The mean tumor thickness was 2.31 mm (5th-95th percentile range: 0.41-6.0 mm). The sentinel lymph node positivity rate was 23.0%. Logistic regression, support vector machine, single tree and decisional tree forest predictive models obtained encouraging rates of NPV (94%, 94%, 94%, and 97% respectively), reduction of SNB procedures (26%, 28%, 27%, and 18% respectively) and false negativity (1.5%, 1.5%, 1.5%, and 0.5% respectively). All models significantly reduced the number of "unnecessary" SNB procedures: in fact, using the above predictive tools the overtreatment rates would be 55%, 53%, 54% and 62%, respectively. Conclusions Using commonly available clinico-pathological variables, predictive models can preoperatively identify a significant proportion of patients (25%) who are at very low risk of sentinel node metastatic disease and thus who might be spared SNB, with an acceptable (1%) risk of being understaged. If validated in large prospective series, these models might be implemented in the clinical setting for more accurate patient selection, which ultimately would lead to better quality of life for patients and optimization of financial resource allocation.

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Clinical Outcome after Sentinel Node Biopsy in 1,313 Patients with Cutaneous Melanoma: An Italian Multicentric Study (SOLISM–IMI) C.R. Rossi,[1]* G.L. De Salvo,[2] M.C. Montesco,[3] A. Testori.[4] *1. Department of Oncological and Surgical Sciences, University of Padova, Padova, Italy; 2. Clinical Trials and Biostatistical Unit, Istituto Oncologico Veneto-IRCCS, Padova, Italy; 3. Department of Pathology, University of Padova, Padova, Italy; 4. Melanoma Unit, European Institute of Oncology, Milano, Italy.*

Background An observational multicentric Italian trial on sentinel node biopsy (SNB) was performed. We investigate herein on: 1) the false negative (FN) rate, 2) possible correlations between prognostic factors and Sentinel Node (SN) and non-SN status, 3) patients' prognosis after SNB. Patients and methods From January 2000 to December 2002, 1,313 consecutive patients with primary cutaneous melanoma were enrolled by 23 centers. Lymphoscintigraphy, blue dye lymphatic mapping, pathological examination and follow-up were performed according to the protocol. Results The SN identification rate was 99.3% . The mean number of SNs was 2.0 (range, 1–17) and only 1 node was removed in 45.4%. The positivity and false-negative rates were 16.9% and 18.4%, respectively (median follow-up, 4.5 years). At multivariable logistic regression analysis, the frequency of positive nodes increased with increasing Breslow's thickness ($p<0.0001$) and Clark level ($p=0.047$) and decreased in female sex ($p=0.007$) and patients with melanoma regression ($p=0.0002$). The presence of macrometastasis was associated with an increasing number of positive SN ($p= 0.009$) only. The 5-year survival of patients with positive sentinel nodes was 70.6% in those with only one positive node and 55.6% when 2 or more nodes were positive ($p= .043$). Multivariable Cox regression analysis indicated that status of SN is the most important prognostic factor (HR=3.08) and that sex, age, Breslow and Clark maintain statistically significant relevance. Ulceration, which was associated with survival when considered as single factor ($p< .0001$) had no impact on survival in the multivariable analysis. By considering SN and non-SN, including FN cases, we identified three groups of patients with different prognosis.. Conclusions The FN rate of SNB is around 20% (when correctly calculated); regression in the primary melanoma seems to be a protective factor from metastasis in SN; macrometastasis seem to influence the number of positive nodes; SNB makes it possible to assess the best prognosis of patients; FN and patients with metastasis at completion lymph node dissection have the worse prognosis.

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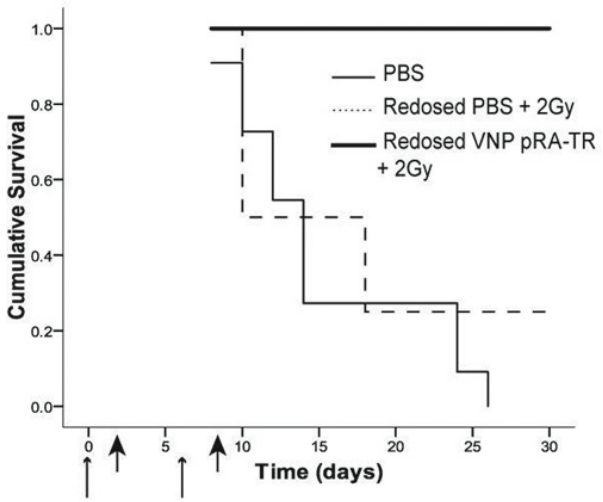
Tumor-Targeted Delivery of TRAIL Using Salmonella typhimurium Enhances Breast Cancer Survival S. Ganai,[1]* R.B. Arenas,[1] N.S. Forbes.[2] *1. Baystate Medical Center / Tufts University School of Medicine, Springfield, MA; 2. University of Massachusetts Amherst, Amherst, MA.*

Background: An ideal cancer therapeutic must selectively accumulate within tumor, have limited toxicity, and be easily eliminated from the host. Attenuated Salmonella typhimurium, a nonpathogenic facultative anaerobe, has been demonstrated as a novel anticancer agent because of its favored growth within tumors. In order to allow spatiotemporal control of cytotoxic protein delivery into tumors, a radiation-inducible gene expression system for secretion of TNF-related apoptosis-inducing ligand (TRAIL) was developed. Methods: Prokaryotic expression plasmids for TRAIL and a green fluorescent protein using the RecA promoter were electroporated into the msbB- purI- strain, VNP20009. In a syngeneic murine model of mammary carcinoma using Balb/c mice, the effect of systemic infection of bacterial vectors with induction by 2Gy gamma radiation at two days after colonization was assessed, examining outcomes of tumor growth and 30-day survival. Results: In vitro confirmation of extracellular TRAIL secretion and caspase-3 and caspase-8 activity were confirmed, with a significant increase in cell death measured by flow cytometry ($p<0.05$). The expression vector for TRAIL induced by radiation led to a significant delay in tumor growth and improved 30-day survival in the mouse model, with a hazard ratio of 0.24 (95% confidence interval, 0.08 – 0.75; $p<0.05$) in comparison with an irradiated control. Repeated dosing and irradiation after one week limited tumor growth from baseline, with a significant survival benefit from 0 to 100% at one month after initial treatment ($p<0.05$). Conclusions: By capitalizing on the intrinsic motility of bacteria and their preferential accumulation within tumors, the therapeutic utility of targeted therapy using attenuated S. typhimurium as a TRAIL expression vector has been demonstrated as an effective method to reduce tumor growth and improve host survival.



Survival curves after PBS, or two doses of PBS + XRT or VNP pRA-TR (small arrow) + XRT (large arrow). At one month, 100% of mice survived with two treatments of VNP pRA-TR + 2Gy, compared to 25% after repeated dosing with PBS + 2Gy, and no survival in the PBS control group ($p<0.05$).

P103

Induction of apoptosis in Melanoma Cells by Non-Thermal Atmospheric Plasma Discharge R. Sensenig,[1]* S. Kalghatgi,[1] A. Goldstein,[2] G. Friedman,[1] G. Friedman,[1] A. Brooks.[1] *1. Surgery, Drexel University College of Medicine, Philadelphia, PA; 2. Stony Brook, Stony Brook, NY.*

Objective: To investigate the role of N-acetylcysteine (NAC) as a possible inhibitor or/modulator of the apoptotic properties of non-thermal atmospheric plasma discharge (PLASMA) in melanoma cells. Introduction: Apoptosis is a critical element in cell regulation. With the development of PLASMA, we sought to evaluate an electrochemical approach to apoptosis induction. PLASMA operates in open air at room temperature sparing tissue from thermal desiccation while biological processes are initiated. To date there has been no investigation of the interaction between PLASMA and the induction of apoptosis. Methods: The PLASMA system consists of a Teflon® coated probe connected to a power supply suspended over the cell surface for the duration of the treatment. Melanoma cells were treated with increasing exposures to PLASMA and evaluated by Trypan blue exclusion test, TUNEL® analysis, and Annexin staining to determine viability and apoptotic activity. To evaluate the role of nitric oxide in the apoptotic mechanism, N-acetylcysteine (NAC), a free radical scavenger, was added prior to plasma treatment. Results: Earlier experience in our lab demonstrated that PLASMA induces apoptosis. If apoptosis induction is due predominately to a nitric oxide effect, we would expect to see an overall decrease in apoptotic activity from the cells pretreated with NAC. Results demonstrated that pretreatment of cells with .225mM NAC prior to PLASMA exposure produced a significant decrease in early apoptotic activity ($p<0.05$), a significant increase in late apoptotic activity ($p<0.05$), yet overall no change in total apoptotic activity. At 2.5mM NAC these results were the same. Conclusion: Exposure of melanoma cells to a sublethal dose of PLASMA induces apoptosis. NAC may decrease early apoptosis associated with PLASMA exposure, but does not provide complete protection against apoptosis suggesting that nitric oxide production is not the main mechanism of this pathway.

Effect of NAC on PLASMA exposure

	%live cells	%early apoptotic cells	%late apoptotic cells	%total apoptotic cells
5 sec. PLASMA tx	72.4%	19.7%	6.9%	26.6%
5 sec. PLASMA tx + 0.225 mM NAC	60.9%	6.6%	18.4%	25.1%
5 sec PLASMA tx + 2.25 mM NAC	56.1%	8.8%	21.3%	30.2%

P104

Minimally Invasive Surgery for Childhood Cancer R.K. Cribbs,* M.L. Wulkan, K.F. Heiss, K.W. Gow. *Surgery, Emory University, Atlanta, GA.*

Background: While minimally invasive surgery (MIS) is well described in adults, its application for childhood cancer is limited. Methods: A retrospective review was recently completed of the MIS procedures performed for cancer diagnosis or resection in a single institution. Type and purpose of procedure, pathologic diagnosis, involvement of specimen margins, conversion to open procedure and postoperative complications were recorded. Results: Between August 1995 and August 2007, there were a total of 155 procedures – 83 thoracoscopic and 72 laparoscopic - performed in 134 pediatric cancer patients. Thoracoscopy was performed for biopsy in 54 (65%), resection in 24 (29%), and staging in 5 (6%). All biopsy specimens obtained were adequate for pathologic diagnosis. The laparoscopic procedures were performed for biopsies in 31 (43%), resection in 31 (43%), supportive care in 7 (10%), staging in 2 (3%), and others in 2 (3%). Only one laparoscopic biopsy failed to provide diagnostic tissue leading to a repeat laparoscopic procedure wherein diagnostic tissue was obtained. The successful biopsy rate was 96.8%. Tumor resection was completed by MIS in 38 of 55 (69%) with the remaining 17 requiring open conversions. Of all 156 procedures performed by MIS, 24 (15%) were converted to open procedures with 15 thoracotomies and 9 laparotomies. There were no recorded complications attributable to the MIS procedure at 1.5-year median post-operative follow-up. There were no port-site metastases during the period of this study. Conclusions: The use of MIS in childhood cancer is safe and effective for biopsy and resection. Future studies are warranted to define the advantages and disadvantages as compared to open procedures.

P105

Results of a Phase II Multicenter Study of Radiolabeled Mannose-Binding Protein (Lymphoseek®) for Lymphatic Mapping in Patients with Breast Cancer and Melanoma J. Kim,[1]* M. Ross,[2] M. Faries,[3] S.P. Leong,[4] C.R. Scoggins,[5] R. Orahood.[6] *1. Division of Surgical Oncology, Case Medical Center, Cleveland, OH; 2. MD Anderson Cancer Center, Houston, TX; 3. John Wayne Cancer Institute, Santa Monica, CA; 4. University of California, San Francisco, San Francisco, CA; 5. University of Louisville, Louisville, KY; 6. Neoprobe Corporation, Columbus, OH.*

Background: Despite widespread use, radiolabeled sulfur colloid is not FDA approved for lymphatic mapping. Lymphoseek is a low molecular weight dextran coupled with mannose with affinity for the mannose-binding protein receptor expressed on lymph node antigen-presenting cells. The purpose of this Phase II study was to determine the safety and efficacy of technetium-labeled Lymphoseek in lymphatic mapping in patients with primary breast cancer and cutaneous melanoma. Methods: 99m-technetium was labeled to Lymphoseek in the nuclear pharmacy at each institution immediately prior to injection in eligible patients with breast cancer or melanoma. Injection technique, lymphoscintigraphy, use of blue dye and sentinel node biopsy was performed by each investigator as per individual standard practice. Results: Eighty patients were enrolled onto the study consisting of 49 patients with melanoma and 31 patients with breast cancer. Five serious adverse events were associated with the study, but none were related to the drug. Overall, the migration of Lymphoseek and mapping to at least one regional lymph node was 76 of 80 patients or 95%. In patients with cutaneous melanoma, 47 of 49 (95.7%) demonstrated a radioactive lymph node. In patients with breast cancer, 27 of 29 (93.5%) demonstrated a radioactive lymph node. The proportion of patients who demonstrated migration of Lymphoseek to a lymph node which was also blue was 96% (49 of 51). Finally, the proportion of patients with radioactive nodes containing metastatic disease was 22.4% and 22.6% in melanoma and breast cancer patients respectively. Conclusions: The results of this Phase II study demonstrate the safety and efficacy of radiolabeled Lymphoseek for use in lymphatic mapping. The high concordance between migration of radiolabeled Lymphoseek to the blue node and the identification of metastatic disease within the nodes suggests that the true sentinel node is being identified. Lymphoseek has the potential to be the first FDA approved radiolabeled lymphatic mapping agent for use in patients with breast cancer and melanoma.

P106

The Surgical Management of Sacral Chordoma J.H. Schwab,[2] J.H. Healey,[1] P.J. Boland.[1]* *1. Memorial Sloan Kettering Cancer Center, New York, NY; 2. Massachusetts General Hospital, Boston, MA.*

Background: Sacral chordomas are rare tumors of the axial skeleton. The purpose of this study was to evaluate factors that contribute to improved local control and survival. In addition we sought to define the expected morbidity associated with removal of these tumors. Methods: 42 patients underwent surgical treatment for sacral chordoma between 1990 and 2005. There were 12 female (30%) and 30 male (70%) patients. The proximal extent of the sacrectomy was at S2 or above in 32 (76%) patients. Results: Follow up averaged 46 months (range 1-169, minimum 2 years or until death). Median survival was 84 months (S.E. 25; 95% C.I. 34-132). The 5 year disease free survival was 56% (S.E. 0.1). The 5 year disease specific survival was 77% (S.E. 0.08). Local recurrence occurred in 17 (40%) patients and metastasis occurred in 13 (31%). Local recurrence ($p=0.0001$), metastasis ($p=0.0001$), prior resection ($p=0.046$) and high grade lesions ($p=0.05$) were associated with a worse disease specific survival. Prior resections were also associated with a higher rate of local recurrence ($p=0.0001$). Intralesional resections had a negative impact on local recurrence ($p=0.01$) and disease specific survival ($p=0.0001$). Wide contaminated margins treated with adjuvant cryosurgery and/or external beam radiation were not associated with a higher local recurrence rate with the numbers available. Ten patients required reoperation due to wound complications. Rectus abdominus myocutaneous flap were associated with decreased wound complications($p=0.01$). Thirty one (74%) patients needed to self catheterize, 16(38%) patients required bowel training and bulk forming agents to facilitate bowel movements, and an additional 12(29%) patients had a colostomy. Twenty eight(67%) patients reported having sexual dysfunction. Two(5%) patients died in the peri-operative

period. Conclusions: Intralesional resection should be avoided as it is associated with a higher local recurrence rate and worse survival. Rectus abdominus myocutaneous flaps ought to be considered as they lower the wound complication rate. These patients have a high morbidity and mortality related to the extent and location of the tumor.

P107

Effect of Geographic Factors on Sarcoma Patient Follow-up Intensity K.S. Virgo,[1] S. Sarkar,[2] A.L. Beitler,[4] J.F. Gibbs,[4] K. Sakata,[2] A. Goel,[1] M.E. Christy,[1] R.A. Audisio,[3] W.G. Kraybill,[4] F.E. Johnson.[1]*
1. Surgery, Saint Louis University, St. Louis, MO; 2. St. Louis Veterans Affairs Medical Center, St. Louis, MO; 3. University of Liverpool, Liverpool, United Kingdom; 4. Roswell Park Cancer Institute, Buffalo, NY.

Introduction: About 1% of all cancers are soft tissue sarcomas (STS); about 60% of these occur in the extremities. Most recurrences (80%) occur within 2 years after potentially curative treatment, but recurrence at ≥5 years is not uncommon. Surveillance programs are designed to identify recurrence, new primary cancers, and complications of therapy early enough to increase survival duration and quality of life. The intensity of surveillance varies among surgeons. We hypothesized that geographic factors would account for much of this variation. Methods: The members of the Society of Surgical Oncology (SSO, N=1592) were surveyed regarding their personal postoperative STS surveillance strategy using standardized clinical vignettes and a questionnaire based on the vignettes. Practice patterns were analyzed by U.S. Census Region, Metropolitan Statistical Area (MSA), and managed care organization (MCO) penetration rate, using repeated measures analysis of variance. The study endpoint was surveillance intensity. Results: 45% of SSO members (714) completed the survey; 343 (48%) perform STS surgery. Of those who perform surgery, 318 (93%) follow their patients long-term. Mean follow-up intensity for the 12 surveillance modalities on the questionnaire was highly correlated with tumor size, grade, and year post-surgery. Controlling for tumor stage, grade, and year post-surgery, the practice location of the surgeon infrequently impacted surveillance intensity. MSA was a significant ($p < .05$) predictor of office visit frequency. MCO penetration rate significantly predicted the frequency of urinalysis and tumor-site MRI. U.S. Census Region significantly predicted the frequency of LFTs. Two-way interaction effects were frequently significant. Few three-way interactions were examined due to sample size limitations. Conclusions: Geographic factors do not generally predict self-reported surveillance practice patterns for patients after curative-intent STS surgery. The overall variation in follow-up intensity appears to reflect factors not evaluated, such as the absence of high-quality evidence supporting any particular strategy and the quality of patients' insurance.

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Intraabdominal Visceral Angiosarcoma (IAVA): Experience from a Major Referral Center D.M. Wang,[2]* A. Lazar,[1] D. Chelouche Lev,[1] D. Tuvin,[1] B.W. Feig,[1] J.N. Cormier,[1] K.K. Hunt,[1] S. Patel,[1] R.S. Benjamin,[1] R.E. Pollock,[1] P. Pisters.[1] *1. Enterprise Services, University of Texas M.D. Anderson Cancer Ceneter, Houston, TX; 2. Yijishan Hospital, Wannan Medical College, Anhui, China.*

Backgound: Angiosarcoma is an uncommon type of soft tissue sarcoma which accounts for only 1% of all sarcomas. IAVA is an extremely rare subtype of angiosarcoma. Most reports have grouped IAVA with cutaneous angiosarcoma and thus the natural history of IAVA has not been well characterized. Design - Retrospective. Methods: We analyzed the medical records of 27 patients with biopsy proven and secondarily confirmed IAVA who were evaluated and treated at our center between 1987-2007. Results: Twenty-seven patients presented with IAVA: 22 patients with primary (localized) disease and 5 patients with metastatic disease. Sites of primary disease included the liver (n=8), adrenal gland (n=5), spleen (n=4), ovary (n=1), kidney (n=1), bladder (n=1), and small bowel (n=1). Among the 22 patients with primary disease, 14 underwent primary tumor resection with curative intent; 8 were treated with palliative chemotherapy. For the subset of patients treated by primary tumor resection, the median follow-up is 37 mos (11-97 mos). Eleven patients (11/14) developed disease recurrence with sites of recurrence including regional, liver, lung, and bone. The median time to identification of recurrence was 7 months (range 1-32 mos). For the 22 primary IAVA cases, the 2-year disease free survival (DFS) and overall survival (OS) were 4.5% and 31.8%, respectively. The 5-year DFS and OS of primary IAVA were 4.5% and 4.5%, respectively representing a single patient (1/22) with primary IAVA who remains alive and free of disease 97 months after diagnosis. Two patients (2/5) with metastatic IAVA remain alive and disease free for more than 5 years after treatment that included primary and metastatic lesion resection, radiofrequency ablation, and chemotherapy. Conclusions: IAVA is a unique form of angiosarcoma. Primary intra-abdominal visceral angiosarcoma is a highly malignant tumor mainly involving the solid organs in the abdomen with disappointing treatment outcomes. Some patients with metastatic IAVA can achieve long-term survival with aggressive treatment. Progress in this disease will require improved understanding of IAVA biology and improvements in systemic therapy.

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Pregnancy-Associated Desmoid Tumors: A Distinct Clinical Entity F.G. Rocha,[1]* S. George,[2] C. Fletcher,[3] M.M. Bertagnolli,[1] J. Butrynski,[2] G. Demetri,[2] J. Morgan,[2] A. Wagner,[2] C.P. Raut.[1]
1. Surgery, Brigham and Women's Hospital, Boston, MA; 2. Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; 3. Pathology, Brigham and Women's Hospital, Boston, MA.

Introduction: Desmoid tumors (DT) are rare soft tissue neoplasms that do not metastasize but are locally aggressive with high recurrence rates after resection. DT are often associated with either familial adenomatous polyposis (FAP) or pregnancy. FAP-associated DT are generally multifocal and recurrences are common (as high as 85% in some series). Pregnancy-associated DT are less well characterized. We sought to determine the natural history and outcome of pregnancy-associated DT. Methods: We reviewed our experience with DT diagnosed during pregnancy between 1990 and 2005. Tumor characteristics, therapy, outcomes and recurrence rates were examined. Results: Of the 207 consecutive patients with DT treated at our institution, 16 were identified with pregnancy-associated DT. None had colonic polyposis suggestive of FAP. Tumors were extraabdominal in 12 (75%) and intraabdominal in 4 (25%). Resections were R0 in 9 (56%) and R1 in 7 (44%); none had R2 resections. Two received adjuvant chemotherapy, and one received postoperative radiation therapy. Postoperatively, five patients were maintained on NSAIDs (4 after R0 resection, one after R1 resection) while one received tamoxifen (after R1 resection). With a median follow-up of 39 months (range 1-115), only 2 (12.5%) recurrences were identified, both after R1 resections. Both underwent re-excision and are currently disease-free. At last follow-up, all were alive and disease-free. One patient has had a subsequent pregnancy with no disease recurrence. Conclusions: Patients with pregnancy-associated DT can usually undergo complete macroscopic resection. Recurrences are rare, especially after R0 resections. This is in part due to their more easily operable, extraabdominal location. Longer follow-up and larger studies with comparisons to comparable non-pregnant patients with DT are necessary to determine if pregnancy-associated DT represent a less aggressive subtype of DT or one benefiting from a more favorable location.

Pregnancy-Associated Desmoid Tumors

Characteristics		Number of Patients N=16 (%)
Age	Median	32.3 years
Size	Mean	9.3 cm
	Range	2.2-21.0 cm
Location	Intraabdominal	4 (25%)
	Extraabdominal	12 (75%)
Extent of Resection	R0	9 (56%)
	R1	7 (44%)
Additional Surgery	Multiple Operations to Remove Primary	3 (19%)
	Reconstruction	4 (25%)
Adjuvant Therapy	Chemotherapy	2 (12%)
	Radiation	1 (6%)
	NSAIDs	5 (31%)
	Tamoxifen	1 (6%)
Recurrence		2 (12%)

P110

Well differentiated vs dedifferentiated liposarcomas: Two distinct diseases requiring distinct treatment approaches G.J. Lahat,* D.A. Anaya, D. Tuvin, P.W. Pisters, D. Lev, R.E. Pollock. *surgical oncology, MDACC, Houston, TX.*

Introduction: Division of retroperitoneal liposarcoma (RPLS) into well differentiated (WD) and dedifferentiated (DD) subtypes is widely accepted; however, WD and DD are usually treated in similar manner. We hypothesized that WD and DD have distinct biologic behaviors and should therefore be treated differently. Methods: A prospective Sarcoma database identified all RPLS patients treated between 1996- 2007. Patients were stratified as either WD or DD and analyzed for recurrence rate, recurrence free survival (RFS), and overall survival (OS). Results: 301 patients were evaluated; 148 patients had curative intent surgery for primary or recurrent RPLS: 77 DD (52%) and 58 WD (39.2%). All were large (DD: 17cm vs WD: 20cm). At presentation, WD were mostly primary whereas DD were mostly recurrent (75.9% vs 41.6%; $p<0.05$). A significant proportion of DD (37.7%) received pre- or postoperative chemotherapy compared to WD (1.7%; $p<0.05$). DD were treated with IORT (9.1%) vs none of the WD ($P<0.05$). Multivisceral resection was more common in DD compared to WD (44.4% vs 26%; $p<0.05$). Equivalent gross total resection rates were achieved (WD: 86.2%; DD (85.7%). Positive margin rates also did not differ (WD: 37.9%; DD: 42.9%). Median follow-up for WD and DD was 38 (range 2-133) and 26 months (range 1-102) respectively. Overall and local recurrence were higher in DD vs WD (81.1% vs 50% and 70.2% vs 43.1%; $p<0.05$). Only 2.7% of WD recurred as high grade metastatic disease. Median RFS and OS were 15.2 and 38 months in WD vs 11.2 and 26 months in DD ($p<0.05$). OS (1, 2 and 5 year) was higher in WD than DD (96% vs 75%; 93% vs 64%; 80% vs 19%; $p< 0.0001$). Conclusion: WD and DD have distinct biologic behavior. Gross total resection is achievable in most WD; unlike DD, high grade recurrence is uncommon. Treatment should therefore reflect these biologic differences so as to maximize survivorship while avoiding unnecessarily extensive resection.

statistically significant differences between WD and DD

Variable	WD (n=58) Number (%)	DD (n=77) Number (%)	p value
Primary tumor recurrenttumor	44 (75.9%) 14 (24.%)	45 (58.4%) 32 (41.6%)	p=0.035
multi focal	6 (10.3%)	20 (26%)	p=0.023
Any chemotherapy	1 (1.7%)	29 (37.7%)	p=0.0001
IORT	7 (9.1%)	0 (0%)	p=0.029
Overall recurrence	27 (50%)	60 (81.1%)	p=0.031
local Recurrence	25 (43.1%)	52 (70.2%)	p=0.042
Recurrence as HG liposarcoma	2 (2.7%)	18 (24.3%)	p=0.0001
median time to recurrence(months) OS (1,2 ,5 year)	15.2 96%,93%, 80%	11.2 75%,64%, 19%	p=0.004 p=0.0006

Abbreviations: WD-well differentiated liposarcoma;DD-dedifferentiated liposarcoma;HG-high grade;LPS-liposarcoma;OS-overall survival

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Single Institution Results from Minimally Invasive Esophagectomy K.L. Meredith,[1]* J. Lewis,[1] M. Melis,[1] J. McLoughlin,[1] E. Siegel,[1] M. Dean,[1] E. Sommers,[1] R. Karl,[2] S. Kelley.[1] *1. H. Lee Moffitt Cancer Center, Tampa, FL; 2. University of South Florida, Tampa, FL.*

Introduction: The incidence of esophageal cancer is increasing in the western world and often portends a poor prognosis even in patients deemed cured by surgery. While the type and extent of operation remains controversial, esophagectomy is traditionally performed via an open technique. Recently, minimally invasive esophagectomy has been shown to be safe while potentially decreasing morbidity. We report our experience with minimally invasive esophagectomy. Methods: We retrospectively reviewed charts from patients who underwent either open (OE) or minimally invasive (MIE) esophagectomy from 2005 to 2007. Statistical comparisons of estimated blood loss (EBL), operative time (OT), complication, length of hospitalization (LOH), mortality, recurrence, pathologic response to chemotherapy, and age were made using Fisher's exact test. Results: We identified 145 patients treated with OE (n=73) or MIE (n=72) with a median age of 66 years (28-83). The mean operative time in the OE was 3.9 hours compared to 5 hours in the MIE patients (p=ns). The mean EBL was 185 ml in OE and 202 ml in patients undergoing MIE (p=ns). The median LOH in patients undergoing OE was 10.5 days compared to 10 days (5-52) in the MIE group (p=ns). Patients who developed a complication had prolonged LOH compared to patients without complications (p=0.00006). There were 3 (4%) leaks in the OE and 5 (7%) in the MIE (p=ns). The MIE exhibited a higher incidence of overall pulmonary complications (effusions, pneumonia) than the OE (p=0.0002). We identified 3 (2%) in hospital deaths amongst both groups. There were 10 (13.8%) recurrences in the MIE group. There were fewer recurrences in patients who demonstrated a complete or partial response to neoadjuvant therapy (p=0.03). Conclusions: MIE is a safe approach to malignant diseases of the esophagus. Comparisons with OE show equivalent complication rates, EBL, LOH, OT, and mortality. However, pulmonary complications appear to be higher with the minimally invasive approach than previously reported. Complete or partial response to neoadjuvant therapy is associated with improvement in disease free survival. These issues warrant further investigation in larger multi-institutional studies.

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Gender Differences in Presentation, Treatment and Outcome of Operable Central Lung Tumors C.P. Parungo Erkmen,* M.T. Jaklitsch, Y.L. Colson. *Surgery, Brigham & Women's Hospital, Brookline, MA.*

Gender differences have come to the forefront of lung cancer management. Our purpose was to examine gender-related differences of presentation, treatment and outcome in the subset of patients with operable central lung tumors. Methods: A nonrandomized, retrospective review was performed of patients with central lung cancer eligible for a sleeve lobectomy or pneumonectomy during the period of January 1990 to January 2002. Preoperative morbidities, tumor type and stage were compared between men and women, as was postoperative length of stay, postoperative morbidities, 30-day mortality, recurrence and death at 4 years post op. Significance was determined with chi square test with discrete variables and student's T test for continuous variables. Results: Of 153 eligible patients (65 women, 88 men), women were younger (55.6 vs. 62.7, $p<0.015$), less likely to have a smoking history (52% vs. 74%, $p<0.01$), coronary artery disease (3% vs. 20%, $p < 0.025$), diabetes (5% vs. 20%, $p < 0.01$) and peptic ulcer disease (2% vs. 13%, $p<0.01$). Women most commonly presented with adenocarcinoma (n= 26, 40%) while men presented with squamous cell carcinoma (n=50, 57%). The distribution of women and men to Stage I through IV was equal as was the distribution to sleeve lobectomy and pneumonectomy. There was no statistical difference between women and men in length of hospital stay (8 days), morbidity (42% vs. 49%), 30-day mortality (6% vs. 2%), recurrence (28% vs. 24%) or survival (49% vs. 35%). The only postoperative gender difference was the increased incidence of atrial fibrillation in women receiving pneumonectomy over sleeve resection (39% vs. 10% respectively, $p < 0.01$). In contrast, men receiving pneumonectomy and sleeve resection had nearly equal incidences of arrhythmia (28% and 28% respectively). Conclusion: Of patients with operable central lung tumors, women presented at a younger age, with fewer co-morbidities. Despite these apparent advantages, postoperative morbidity, short-term and mid-term mortality were equivalent. The only gender difference in postoperative morbidity was the increased likelihood for women to experience atrial fibrillation after pneumonectomy.

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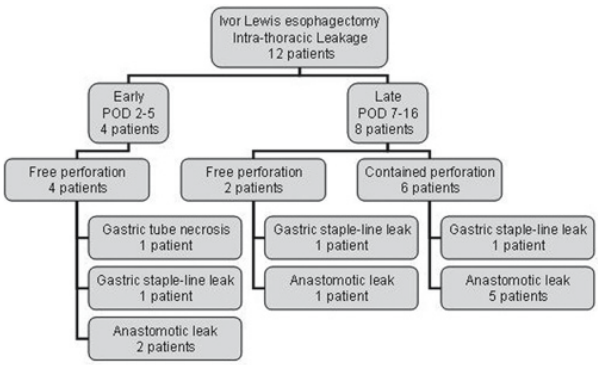
"Anastomotic" Leakage After Esophagectomy for Carcinoma. A Mortality-Free Experience A.I. Sarela,[1]* D.J. Tolan,[2] K. Harris,[2] H.M. Sue-Ling,[1] S.P. Dexter.[1] *1. Department of Upper Gastrointestinal Surgery, Leeds Teaching Hospitals, Leeds, United Kingdom; 2. Department of Radiology, Leeds Teaching Hospitals, Leeds, United Kingdom.*

Introduction: Leakage is a serious complication of esophagectomy and is historically associated with high mortality. This study aimed to describe the surgical anatomy of leaks and strategies for clinical-management. Patients & Methods: A prospectively maintained database from July 2002 to July 2005 at a referral unit for foregut cancer was used to identify patients with leakage of saliva or gastrointestinal content, following esophagectomy and reconstruction with stomach. Contrast swallow was routinely performed on post-operative day 7. Leakage was diagnosed and classified by well-defined criteria. Results: There were 99 men and 27 women, yielding an institutional volume of 42 esophagectomies/year. There was no in-hospital mortality from any cause. Actual one-year survival was 87%. An Ivor Lewis operation was performed on 103 patients (82%); four patients had leakage within 5 days of operation and all had immediate re-thoracotomy. Further eight patients with Ivor Lewis operation had leakage after day 5 (median POD#9; maximum POD#16) and this was detected by contrast-swallow in only three patients; two patients had no intervention, four patients had radiology-guided drainage, one had thoracoscopy and one had re-thoracotomy. Leakage was from the actual esophagogastric anastomosis in eight patients or from the linear gastric-staple line in three patients or due to gastric necrosis in one patient. Twenty-three patients had a transhiatal or three-incision operation; leakage was from the actual anastomosis in five patients or due to gastric necrosis in one patient. 38% of patients with actual anastomotic leakage required admission to the intensive care unit as compared to 75% of patients with gastric-tube leakage. The median hospital stay was 31 days with anastomotic leakage as compared to 45 days with tube leakage. Conclusions: Following Ivor Lewis esophagectomy, leakage was from the actual anastomosis in two-thirds of patients or from the gastric conduit in the remaining one-third. Prompt re-operation is recommended for early post-operative leakage whereas most patients with leakage after day 5 may be treated non-operatively.



Patters of Leakage After Ivor Lewis Esophagectomy

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Laparoscopic resection of residual retroperitoneal tumor mass of testicular cancer after chemotherapy; a surgical breakthrough in testicular cancer treatment R.M. Krol,[1]* R.J. Ginkel,[1] H.S. Hofker,[1] H.S. De Jong,[1] J.A. Gietema,[2] H.J. Hoekstra.[1] *1. Surgical Oncology, Groningen University Medical Center, Groningen, Netherlands; 2. Medical Oncology, Groningen University Medical center, Groningen, Netherlands.*

Introduction. One of the cornerstones of successful testicular cancer treatment is resection of residual retroperitoneal tumor mass (RRRTM) after cisplatin based polychemotherapy. During the last decade, laparoscopic surgery was introduced in the staging and treatment of various benign and malignant diseases, e.g. laparoscopy is already used in the staging of testicular cancer. The opportunities of laparoscopic RRRTM (L-RRRTM) of testicular cancer were explored in patients with minimal residual disease after induction chemotherapy. Patients and methods. Between January 2005 – July 2007 20 patients, median age 26 (range 16-41) years, Royal Marsden Classification 2 stage IIA (10%), 11 stage IIB 11 (55%), 3 stage IIC (15%), 4 stage III N2 (20%), underwent L-RRRTM and were prospectively studied. Results. The median tumor size of residual tumor mass was 22 (range 11-46) mm. The median operative time was 205 (range 148-325) minutes, including positioning of the patient. Conversion was necessary in one patient due to a bleeding (conversion rate 5%) and one procedure was hand-assisted (5%). The remaining laparoscopic procedures were completed as planned (success rate 90%). Complications were encountered in one patient (5%), who developed chylous leakage requiring a successful second laparoscopic intervention with laser fulguration. Histological examination of the resected RRTM showed no viable tumor; fibrosis or necrosis in 8 patients (40%), and mature teratoma in 12 patients (60%), all completely resected. The median post-operative hospital stay was one (range 1-4) day. During a median follow up of 9 (range 1-24) months, none of the patients developed a recurrence. The only long-term treatment related complication encountered was retrograde ejaculation in two patients (10%). Conclusion. These results show a new, promising minimal invasive surgical treatment strategy in the combined treatment of testicular cancer, which in carefully selected patients allows adequate resection of RRTM with minimal morbidity, short hospital stay and a quick rehabilitation.

P115

Advanced Stage Renal Cell Carcinoma Treated by Radical Nephrectomy and Adjacent Organ or Structure Resection M.E. Karellas,* T.L. Jang, M.A. Kagiwada, M.D. Kinnaman, W.R. Jarnagin, P. Russo. *Surgery/Urology, Memorial Sloan-Kettering Cancer Center, New York, NY.*

Introduction and Objective Approximately 30% of patients with renal cell carcinoma (RCC) either present with or develop locally advanced or metastatic disease which rarely involves adjacent organs and structures. It was the purpose of our study to exam the impact of radical nephrectomy (RN) with adjacent organ and structure resection Methods We searched our prospective database from July 1989 to April 2006 for patients with pathologic stage T3 or T4 RCC who underwent RN and resection of a contiguous organ or structure. Univariate analysis was performed to compare demographic characteristics. Survival analyses were performed using the Kaplan-Meier method. Results We identified 38 patients out of 2464 (1.5%) who underwent RN with adjacent organ or structure resection. Median age was 63 years (IQR=49, 70 years), median size of the resected mass was 11 cm (IQR=8, 14 cm) and median follow-up after operation was 13 months (IQR=5, 33 months). Twelve patients (32%) were stage pT3, 26 patients (68%) were pT4 stage, 36 of 38 patients (95%) had conventional clear cell renal carcinoma, and 14 patients (37%) had positive margins. The liver (10) was the most commonly resected organ or structure followed by the vertebral body (8), and pancreas and bowel (6). Twenty-seven patients (71%) were dead of disease within the study follow-up period, 3 patients were alive with metastatic disease, and only 1 patient was alive with no evidence of disease at 5 years. The overall mortality rate was 34 of 38 patients (90%). The median time from surgery to death was 11.7 months (IQR=5.4, 29.2 months). The surgical margin status was the only statistically significant factor for recurrence and death (p=0.0061). Conclusions The prognosis of advanced RCC patients with adjacent organ or structure involvement is poor, and similar to patients with metastatic disease. These patients should be thoroughly counseled regarding the impact of surgical management and considered for clinical trials with new targeted systemic agents either before or after surgical resection.

P116

The apoptosis signal ceramide (C6) significantly enhances the anti-tumor effects of a variety of chemo therapeutic drug classes D. Shrayer*(1), M. Resnick*(2), S. Hazelwood*(3), H.J. Wanebo*(4) *Division of Surgical Oncology, Roger Williams Medical Center(1,3,4) *Department of Pathology, Rhode Island Hospital(2) H.J. Wanebo,[1]* D. Shrayer,[2] M. Resnick,[2] S. Hazelwood.[3] *1. Surgical Oncology, Landmark Medical Center, Woonsocket, RI; 2. Roger Williams Medical Center, Providence, RI; 3. Rhode Island Hospital, Providence, RI.*

Introduction: The Ceramides are a major signaling pathway for apoptosis in cells undergoing stress or exposure to chemotherapy. We have previously demonstrated synergistic anti-tumor effects of combining C6 ceramide with Paclitaxel, Doxorubicin and Cisplatin and are currently addressing the question; does C6 augment activity of all the major classes of drugs? Methods: Invivo experiments SCID/Beige/Taconic male mice were inoculated S.C. with 2X106 L3.6 pancreatic cells and treated 4 days post tumor implant with trhice weekly (3x/wk) intraperitoneal (IP) injections of paclitaxel (P) 3.0m/kg, Oxaliplatin (OX) 2.5mg/kg, Cisplatin (CP) 2.5mg/kg, Gemcitabine (Gem) 10mg/kg with/without ceramide 10mg/kg. Mice were observed for 6 weeks and were autopsied when near death. (All controls died by 3rd week). Maximum tumor volume, tumor weight; body weight and survival were recorded. Results: Combination with C6 ceramide augmented the tumor reduction obtained by chemotherapy alone by 57% (while preserving body weight), and increased 6 week survival from 0% (Chemotherapy alone) to 60% with combined therapy. Mean survival was increased from 25 to 37 days. Although short term immunohistochemical studies suggested enhanced apoptosis and increased caspase 3 production by ceramide combinations other pathways may be involved. Conclusion: C6 ceramide significantly enhanced anti tumor effects of the anti microtubule Paclitaxel,a DNA interculating antibiotic (doxorubicin) the alkylating/DNA adducting agents (Cisplatin, Oxaliplatin) and an anti metabolite (Gemcitabine) suggesting generation of broad based apoptotic signals which interact with all the major cancer drug classes (tested).

Effect of C6 Ceramide +/- Chemotherapy on L3-6 Growth in Scid Mice

Drugs	Mean Final Tumor Volume	Mean Survival Time (days)	% Survival @ 3 & 6 wks	Mean Body Weight (g) (Time of Death or sacrifice)
Control	1.56+/-0.2	17.8+/-1/1	0%/0%	17.8
Ceramide	1.69+/-0.3	20.8+/-1.1	40%/0%	17.0
Taxol	1.83+/-0.4	23.0+/-2.4	60%/0%	17.4
Oxaliplatin	1.76+/-0.2	27.4+/-2.2	100%/0%	15.6
Cisplatin	1.83+/-0.1	25.6+/-3.2	60%/0%	16.6
Ceramide & Taxol	1.19+/-0.01 (++)	35.2+/-4.0 (++)	100%/60% (++)	20.0 (++)
Ceramide & Oxaliplatin	0.75+/-0.01 (++)	35.0+/-1.4 (++)	100%/60% (++)	20.0 (++)
Ceramide & Cisplatin	1.16+/-0.01 (++)	40.6+/-1.4 (++)	100%/60% (++)	20.0 (++)
Ceramide & Gemcitabine	0.693 (++)	38.8+/-3.2 (++)	100%/60% (++)	18.6 (++)

Significance +p<0.1,++p<0.05,+++p<0.01

P117

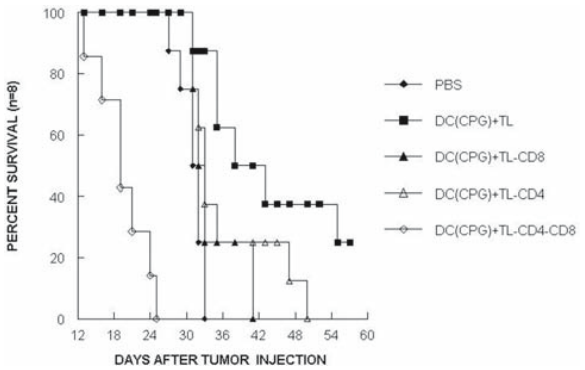
Sigma-2 Receptor Ligands Potentiate other Therapies and Improve Survival in Models of Pancreatic Cancer H. Kashiwagi,[1]* J.E. McDunn,[2] P.O. Simon,[1] P.S. Goedegebuure,[1] Z. Tu,[3] R.S. Hotchkiss,[2] R.H. Mach,[3] W.G. Hawkins.[1] *1. Department of Surgery, Washington University, St. Louis, MO; 2. Department of Anesthesiology, Washington University, St. Louis, MO; 3. Department of Radiology, Washington University, St. Louis, MO.*

Backgroud: We have previously shown that selective sigma-2 ligands bind preferentially to pancreas cancer and induce apoptosis. Other standard (Paclitaxel) and experimental (TAT-BH3) therapies also induce apoptosis. We examined whether the sigma-2 receptor specific ligand (SV119) enhances the effects of other pro-apoptotic therapies. **Methods:** Cancer cell lines (CFPAC, ASPC, Panc1 and Panc02) were incubated with SV119 in combination with Paclitaxel or TAT-BH3 and apoptosis was determined by FACS using TUNEL staining. Controls included vehicle and point-mutated TAT-BH3 inactive peptide. We also studied combination therapy with SV119 and Paclitaxel in an allogenic animal model of pancreatic cancer (n=10 mice per group). Tumor diameter>15mm or ulceration was used as a surrogate for survival. All in vitro experiments were repeated in triplicate. **Results:** SV119, TAT-BH3 and Paclitaxel all induced tumor apoptosis in a dose-dependent fashion in all pancreatic cancer cell lines. TUNEL positive cells ranged from 26.6 to 34.8 % at the highest dose of S2R (10μM) and from 28.4 to 34.4 % with TAT-BH3 (10μM), respectively. Combinations demonstrated dramatic increases in apoptosis. For example, ASPC responded best to a combination of SV119 and TAT-BH3 (61%, TUNEL positive) as compared to no treatment (15%, $p<0.003$), SV119 alone (27%, $p<0.0001$) and TAT-BH3 alone (24%, $p<0.001$). No effect above background was detected in vehicle control or TAT-BH3 inactive peptide treated groups. SV119 (1 mg/mouse/day) was administered in combination with Paclitaxel (300 μg/mouse/day) over 7 days to mice with established tumors. A survival benefit was observed with combination therapy but not with single agents ($p=0.002$). Animals tolerated the combination therapy well and no gross toxicity was observed by serum biochemistry or histologic evaluation of major organs. **Conclusion:** We demonstrate that the combination of Sigma-2 receptor ligand (SV119) with other standard or experimental therapies leads to significant increases in cancer cell death and improves survival without added toxicity. This experimental design highlights a new potential strategy for the treatment of pancreatic cancer.

P118

$CD4^+$ and $CD8^+$ T Cells Contribute to the Effector Phase of Tumor Rejection in a Murine Pancreatic Cancer Model N. Vohra,[2]* S. Pilon-Thomas,[3] D. Osborne,[2] J. Mulé,[3] E.E. Zervos.[1] *1. Department of Surgery, East Carolina University, Greenville, NC; 2. University of South Florida College of Medicine, Tampa, FL; 3. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.*

Introduction: Dendritic cell (DC) based immunotherapy has shown promise in the treatment of solid tumors by inducing anti-tumor immunity. Manipulation of specific T cell subsets has been attempted to augment anti-tumor immunity in various tumor models. Here, we attempt to determine the effect of $CD8^+$ and $CD4^+$ T cells on anti-tumor immunity in a dendritic cell based immunotherapy model of pancreatic cancer. Methods: C57BL/6 mice were vaccinated with PANC02 (a syngeneic pancreatic ductal adenocarcinoma) lysate-pulsed DC matured with CpG (n=32) or PBS (n=8) four times at seven day intervals. One week after the final vaccination, mice were challenged with $3x10^5$ PANC02 tumor cells subcutaneously on the flank. To study effects of $CD4^+$ and $CD8^+$ T cells on tumor rejection, PANC02 lysate pulsed-DC vaccinated mice received either nRatIgG, anti-CD8 monoclonal antibody (mAb), anti-CD4 mAb or both. Depletion was begun three days prior to tumor challenge, continued until the end of the experiment and confirmed using flow cytometry. Results: Depletion of $CD4^+$ and $CD8^+$ T cells using respective monoclonal antibodies was successful. Flow cytometric analysis of splenocytes from mice treated with the appropriate monoclonal antibody showed greater than 95 % depletion of the respective T cell subset. Mice with depletion of both $CD8^+$ and $CD4^+$ T cells demonstrated fastest tumor growth and shortest survival. Depletion of either $CD4^+$ or $CD8^+$ T cells resulted in intermediate tumor growth and survival while mice vaccinated with PANC02 lysate-pulsed DC alone demonstrated the greatest survival benefit. Discussion: Tumor lysate-pulsed DC confer protective immunity in a murine model of PCA. Protection against tumor was decreased by depletion of either $CD8^+$ or $CD4^+$ T cells and completely abrogated by depletion of both, demonstrating that $CD4^+$ and $CD8^+$ T cells are required for the effector phase of tumor rejection.



P119

Isolated Limb Perfusion with Acidic Perfusate Activates eNOS in Xenografted Melanoma Cells D. Han,* T. Du, M.J. Dela Cruz, G.C. Karakousis, I. Prabakaran, M.A. Guvakova, D.L. Fraker. *Hospital of the University of Pennsylvania, School of Medicine, Department of Surgery, Philadelphia, PA.*

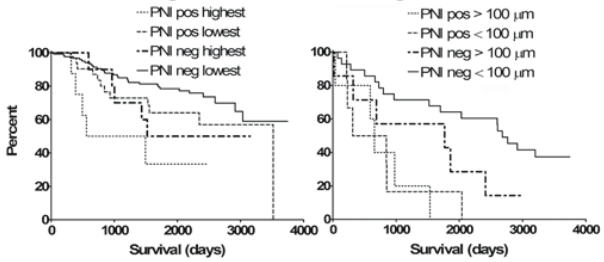
Introduction: Clinical and preclinical studies have shown that acidifying the perfusate during isolated limb perfusion (ILP) increases nitric oxide (NO) production in tumor-bearing limbs and improves tumor response rates. Here we tested the hypothesis that tumor cells in vivo may produce NO as a potential mechanism for the improved tumor responses seen after acidic perfusion. Methods: Nude rats with xenografted NIH1286 human melanoma cells were divided into groups of 3-6 rats consisting of non-treatment (X) and treatment with control saline (C), melphalan (M), acid (A) or melphalan+acid (MA). Average pH values for C/M and A/MA were 7.4 and 6.7. The mRNA and protein expression of nitric oxide synthase (NOS) isoforms: endothelial (eNOS), inducible (iNOS) and neuronal (nNOS) were examined in tumor extracts using two-step quantitative real time PCR (qRT-RCR) and Western blotting (WB). Immunofluorescent staining with antibodies recognizing NOS isoforms was performed on frozen sections of xenografts. Results: Unlike NIH1286 melanoma cells in culture, 100% of melanoma xenografts express human eNOS as shown by qRT-RCR using primers specific for human eNOS mRNA; expression of eNOS protein was confirmed by WB. Levels of eNOS mRNA were significantly higher ($P<0.05$) in xenografted melanoma cells compared with cultured melanoma cells; no significant differences in eNOS mRNA expression between treated xenografted groups were seen (C, M, A, MA). Immunostaining for the activated form of eNOS (pSer1177eNOS) was increased in xenografted melanoma cells in groups A and MA compared with groups X, C, and M. Preliminary data indicate that 14% of melanoma xenografts express iNOS protein with no correlation to ILP treatments seen so far. None of the melanoma xenografts expressed detectable nNOS protein. Conclusion: Xenografted NIH1286 human melanoma cells show increased expression of eNOS, an enzyme generating NO. Furthermore, phosphorylation of eNOS at Ser1177 in melanoma tissues is increased after ILP when perfusates with and without melphalan are acidified. The data suggest that ILP with acidic perfusate likely contributes to NO production in melanoma-bearing limbs by activating eNOS.

P120

Neuroepithelial Interaction in Colorectal Cancer: A Deadly Combination C.A. Liebig,[1]* J.A. Wilks,[1] N. Agarwal,[1] G. Verstovsek,[2] G. Ayala,[2] D. Berger,[1] D. Albo.[1] *1. Surgery, Baylor College of Medicine, Houston, TX; 2. Baylor College of Medicine, Houston, TX.*

Introduction: We have recently shown perineural invasion (PNI) to be an independent prognostic factor for poor outcomes in patients with colorectal cancer (CRC). Furthermore, we recently reported on the novel finding of neurogenesis in CRC. We now hypothesize that PNI and neurogenesis are two components of a phenomenon of neuroepithelial interaction that confers a more aggressive tumor phenotype and worse prognosis in CRC. Methods: All cases of resected CRC at our institution during a 5 year period (n=347) were used to create a tissue array. Paired tumor and normal colon samples from each patient were included in the array. Patient demographic, pathology, tumor stage and overall and disease-free survival (minimum 5 years follow-up) were entered into a database. A blinded pathologist determined the presence/absence of PNI. Nerves were identified by immunostaining for PGP9.5. Neurogenesis was evaluated by measuring nerve density (number of nerves per hpf) and nerve diameters (average of three largest nerves). Survival curves were analyzed using a Kaplan-Meier method and compared by log rank test. Differences between means were analyzed using two-way ANOVA. Results: Patients whose tumors contained PNI and high nerve density had a much lower 5 year survival rate compared to those without PNI and low nerve density (33% vs 78%, respectively; $p=0.003$). Similarly, patients whose tumors contained PNI and large nerve diameters had a much lower 5 year survival rate compared to those without PNI and small nerve diamters (0% vs. 64%, respectively; $p=0.002$). Patients with either PNI or neurogenesis (high nerve density or large nerve diameters) had 5 year survival rates which were less than those without PNI and neurogenesis and greater than those with both (Figure 1). Conclusions: PNI and neurogenesis are two components of a novel phenomenon of neuroepithelial interaction in CRC. When present together, they portend a much worse prognosis. As such, neuroepithelial interaction markers in CRC such as PNI and neurogenesis could be used for therapy stratification purposes.

Figure 1. PNI and Neurogenesis



P121

Activation of the Unfolded Protein Response in Melanoma Cell Lines Exposed to Proteasome Inhibitor-Induced ER Stress C.J. Wray,* K.F. Fournier, D. Sundi, K. Zhu, L. Marquis, D.J. McConkey. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Introduction: Proteasome inhibitors are being investigated as chemotherapeutic agents. Human melanoma cell lines display varying sensitivity to proteasome inhibition which may be related to the unfolded protein response (UPR). Endoplasmic reticulum (ER) stress induces the UPR, activating eIF2α which decreases protein synthesis. This protective mechanism against ER stress has not been fully characterized in melanoma cell lines. Methods: Cell lines A375sm, SB2, WM115 and WM2664 were grown in vitro. Cells were treated with increasing concentrations (0-100nM) of PS-341 or NPI-0052 for 24 hrs. Induction of apoptosis was measured by propidium-iodide flow cytometry. In vitro cell viability was measured with IVIS luminescence imaging (photons/second). eIF2α expression was evaluated by Western blotting after PS-341 or NPI-0052 treatment. Confocal microscopy was used to visualize intracellular aggresome formation. Results: Apoptotic cell populations were higher in A375sm (48.1%) and WM2664 cells (27.5%) following PS-341 treatment (100nM). SB2 and WM115 cell lines were less sensitive to PS-341-induced apoptosis (subdiploid: SB2 4.5% and WM115 2.2%). IVIS imaging detected less luminescence in A375sm (control: 2.57x105 p/s vs. NPI-0052 20nM: 1.77x105 p/s) and SB2 cells (control: 2.74x105 p/s vs. NPI-0052 20nM: 1.70x105 p/s) treated with NPI-0052 for 24 hrs. Western blotting demonstrated equivalent protein expression of eIF2α in all 4 cell lines. However, the PS-341 resistant cell lines (SB2 and WM115) revealed higher levels of active, phosphorylated eIF2α. Confocal microscopy detected increased aggresome formation in the PS-341 sensitive A375sm cells. Conclusions: Melanoma cell lines SB2 and WM115 appear resistant to PS-341. These cell lines phosphorylate eIF2α inducing the UPR. Proteasome inhibitor-sensitive cell lines do not effectively activate the UPR, which may explain aggresome formation in A375sm. Therefore, the UPR appears to be a protective mechanism against ER stress. Cell lines that are not sensitive to proteasome-inhibition may have enhanced alternative protein degradation pathways, which may explain PS-341 or NPI-0052 resistance.

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The Novel Proteasome Inhibitor NPI-0052 Plus TRAIL (TNF Related Apoptosis Inducing Ligand) Activates the Extrinsic Apoptotic Pathway in Pancreatic Cancer D. Sundi,* K. Fournier, C. Wray, D. McConkey. *Cancer Biology, MD Anderson Cancer Center, Houston, TX.*

Introduction: NPI-0052 has been observed to cause cell death in hematologic malignancies with less toxicity than other proteasome inhibitors. The pathway by which combination NPI-0052/TRAIL causes cell death is unknown. The present investigation seeks to establish whether the mechanism of cell death includes the extrinsic receptor-mediated apoptotic pathway in pancreatic carcinoma cells. Methods: Pancreatic cancer cell lines mPanc-96, Panc-1, L3.6pl and HS766T were treated for 12-36 hours with NPI-0052 (0-100 nM), TRAIL (0-200 ng/ml), or both. Drug-sensitive BV bladder carcinoma cells served as positive controls. Induction of apoptosis was measured by propidium iodide-flow cytometry. Lysates were subjected to SDS-PAGE and probed with Caspase 3 and 8 antibodies. Results: Combination treatment with low dose NPI-0052 (10 nM) and TRAIL (10 ng/ml) caused significant cell death as observed with light

microscopy when compared to high doses of either drug alone. For mPanc-96, Panc-1, and L3.6pl cell lines, the apoptotic cell populations with 24h of combination treatment were 20%, 16.7%, and 13.4%, respectively. This finding was confirmed by immunoblots for Caspase 3, a downstream executioner caspase, which is a marker for apoptosis. Caspase 3 immunoblots showed (1) enhancement of cleaved active p16/18 fragments and (2) attenuation of inactive procaspase bands when Panc-1, L3.6pl, and HS766T cells were treated with the NPI-0052 and TRAIL combination. Caspase 8 immunoblots showed (1) enhancement of cleaved intermediate p41/43 fragments in Panc-1 and L3.6pl lysates treated with combination NPI-0052 and TRAIL and (2) enhancement of cleaved active p16/18 fragments in Panc-1 and HS766T cells exposed to the combination treatment. Conclusion: NPI-0052, when combined with TRAIL in several human pancreatic cancer cell lines, activates caspase 8, a component of the extrinsic apoptotic pathway. Future work will examine the role of Caspase 8 regulators FADD, p53, and c-FLIP in NPI-0052/TRAIL-induced apoptosis.

P123

Mechanism of melanoma cell death following arginine depletion
E.C. Hsueh,[1]* S.M. Knebel,[1] C. Hsueh,[3] Y. Leung,[2] W. Lo,[2] P.N. Cheng.[2] *1. Saint Louis University, St. Louis, MO; 2. Hong Kong Polytechnic University, Hong Kong, China; 3. Loma Linda University, Loma Linda, CA.*

Melanoma cells are sensitive to arginine depletion. Absence of activity in some urea cycle enzymes has been observed in human cancer cells. We evaluated the mechanism of action of arginine depletion with recombinant arginase in melanoma cells. Recombinant human arginase (BCT-100) was manufactured by fermentation of a recombinant B. subtilis strain LLC 101 encoded with human arginase gene. Cell viability assay after 72 hour BCT-100 co-culture were performed using tetrazolium salt conversion method in 20 human melanoma cell lines. Urea cycle integrety in 3 BCT-100 sensitive cell lines were evaluated by co-culture with 0.1 U BCT-100 and various concentration of citrulline or ornithine supplement. qRT-PCR for GAPDH, argininosuccinate synthetase (ASS), and ornithine carbamoyl transferase (OCT) genes was performed in triplicate following total cellular RNA extraction. DNA fragmentation was determined using ApoDirect TUNEL assay. Western blot analysis for 4ebp1 and S6k1 phosphorylation were performed following co-culture with BCT-100 ± citrulline supplement. Sensitivity to arginine depletion was observed in all 20 melanoma cell lines. Median EC50 value was 0.02 IU/ ml. TUNEL analysis demonstrated that BCT-100 mediated cell death was not due to direct cytotoxicity via apoptosis pathway. Supplement with ornithine did not abrogate the cytotoxic effect of arginine depletion with BCT-100 on the melanoma cells. However, supplement with citrulline diminished the cytotoxic effect of BCT-100 treatment by 50%. All but 3 melanoma cells had detectable levels of ASS expression above qPCR cycle threshold. In contrast, only 2 melanoma cell lines had minimally detectable OCT expression. Western blot analysis revealed that arginine depletion with or without citrulline supplement resulted in dephosphorylation of mTOR signaling pathway protein, 4ebp1. Addition of rapamycin to BCT-100 co-culture did not enhance the melanoma cytotoxicity of arginine depletion. Arginine depletion resulted in non-apoptotic cell death of melanoma cells. Defect in urea cycle with lack of OCT enzyme predisposed melanomas to arginine depletion sensitivity. The mechanism of action may involve inhibition of mTOR signaling.

P124

Engineering carcinoembryonic antigen (CEA)-specific T cells by TCR gene transfer
J.J. Roszkowski, M.E. Brown, J.A. Guevara, J. McCracken, G.E. Lyons, J.A. O'Sullivan, M.D. McKee.* *The University of Chicago, Chicago, IL.*

Introduction: CEA is expressed by several common human cancers and has been shown to elicit T cell responses from both mice and humans. CEA is therefore a tumor associated antigen (TAA) and a potential target for immunotherapy. T cell receptor (TCR) gene transfer uses retroviral vectors to create tumor reactive lymphocytes by inducing expression of a TCR from a TAA-specific T cell clone. Difficulty generating CEA reactive clones led us to use T cell hybridoma technology for the identification of CEA-specific TCR genes. **Methods:** HLA-A2K^b transgenic mice were vaccinated with modified antigenic CEA:605-613 peptide. Lymph nodes from vaccinated mice were harvested and stimulated once in vitro with vaccinating peptide. Stimulated T cells were fused with BW5147 thymoma cells. Resulting T cell hybridomas were screened for reactivity to T2 cells pulsed with CEA:605-613 by ELISA for IL-2 secretion. Identification of the TCR α and β chains responsible for CEA reactivity was determined by a combination of RT-PCR, flow cytometry, 5' RACE and DNA sequencing. **Results:** Hybridoma 15bD1 was found to secrete IL-2 in response to co-culture with T2 cells pulsed with altered and native CEA:605-613. The TCR β chain was identified as BV5s1 and the TCR α chain as ADV17s2. The TCR α and β chains were cloned by RT-PCR and ligated into a retroviral vector. Retroviral supernatants were generated and used to transduce the TCR- murine thymoma variant BW58α-β- and human donor lymphocytes. TCR transduced BW58cells expressed the transferred TCR on their surface as demonstrated by fluorescent staining of BV5s1 as well as CD3, and recognized A2Kb+ tumor cells loaded with CEA:605-613 peptide but not an irrelevant peptide. Transduced T cells from human PBMC also expressed BV5s1 and showed high avidity recognition of CEA:605-613 loaded T2 cells (<100 pg/ml). **Conclusions:** We have isolated, identified, cloned and transferred a murine TCR capable of recognizing the HLA-A2.1 restricted CEA:605-613 antigenic peptide. The ready availability of CEA reactive T cells through transfer of the 15bD1 TCR is potentially useful for preclinical and clinical studies of adoptive T cell therapy for human adenocarcinoma.

P125

Resistance to oxaliplatin in human intestinal-type gastric cancer cells demonstrates increased levels of angiogenic and tumor stem cell markers
S.J. Lim,* F. Fan, N.A. Dallas, M.J. Gray, L. Xia, S. Samuel, P. Gaur, L.M. Ellis. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Introduction: Oxaliplatin (Ox) is being utilized with increasing frequency for the treatment of gastric cancer. However, its efficacy is limited by the development of resistance. In order to identify potential targets for treatment in Ox resistance, we developed a gastric cancer cell line resistant to Ox and investigated the molecular and phenotypic alterations observed in these cells. Methods: The human gastric cancer cell line MKN-74 (intestinal-type) was exposed to increasing concentrations of Ox to create a stably resistant cell line MKN-74/OXR at 2 μM (clinically relevant dose) over an 8 month duration. Proliferation and chemo-resistance were assessed by MTT assays. Molecular alterations associated with Ox resistance were evaluated by Western blotting and RT-PCR. Boyden chambers were utilized to assess migration and invasion. Results: MKN-74/OxR cells demonstrated an ~2-fold increase in the level of CD44 in MKN-74/OXR cells, a cell adhesion molecule and tumor stem cell marker. VEGF-A and -B levels did not change with Ox resistance. In contrast, both Notch1 (~2-fold) and Jagged-1 (~5-fold), recently discovered mediators of tumor angiogenesis, were upregulated in MKN-74/OxR cells. Surprisingly, MKN-74/OxR cells showed increased sensitivity to 5-fluorouracil (5FU) relative to the parental cell line. In contrast to Ox resistant colon cancer cells (Yang et al. Clin Ca Res 2006), MKN-74/OxR cells did not demonstrate molecular changes associated with epithelial-mesenchymal transition. However, we did note that OxR cells demonstrated increases in migration (~4-fold) and invasion (~33-fold) with no significant change in proliferation ($p < 0.0005$). Conclusion: Ox resistant gastric cancer cells demonstrated increased levels of CD44, Notch-1 and Jagged-1, markers associated with tumor stem cells and angiogenesis. Identification of molecular alterations in chemoresistant cells may help formulate rationale therapeutic strategies for patients who become refractory to primary treatment regimens.

P126

Genomic and Proteomic Analysis of High Risk Cancer Patients
J.A. Kuhn,[1]* S. Steen,[1] N. Senzer,[2] P. Maples,[2] J. Nemunaitis.[2] *1. Surgery, Baylor University Medical Center, Dallas, TX; 2. Mary Crowley Medical Research Center, Dallas, TX.*

Introduction Molecular profiling with gene and/or protein expression signatures has shown evidence of prognostic utility and response-predictive potential in patients with cancer. Identification of key 'highly-connected' proteins acting as routing hubs in cancer networks may present new opportunities for therapeutic intervention. The purpose of this study was a feasibility study of 24 high risk patients for potential targeted molecular therapy. Method Malignant and benign tissue was snap frozen in liquid nitrogen with subsequent laser microdissection to achieve cancer cell density greater than 80%. 2-Dimensional

Difference In-Gel Electrophoresis (2D-DIGE) coupled with mass spectroscopy was then performed to determine differential quantitative protein and oligonucleotide microarray (Affymetric U 133) to determine co-expressed mRNA expression. Results Initial diagnoses included melanoma (n=4), colorectal cancer (n=4), lung cancer (n=10), breast cancer (n=2), prostate cancer (n=1), pancreas cancer (n=1), sarcoma (n=1), and CLL (n=1). Proteomic analysis identified 15-25 up-regulated proteins (≥2-fold) when compared to the comparator benign tissue for each patient. Using as criteria connectivity analysis, high orthology, and network inference engine analysis we identified ANXA2, RACK1, GSN, STMN1, HM23A, and HSP27 as possible therapeutic targets. Microarray analysis confirmed mRNA over-expression. Recognition of key pathway proteins allowed for selective administration of existing molecular-specific therapy in 6 patients based on molecular pathway information. Eligibility for targeted therapy using existing agents would have been possible in 19/24 patients assuming optimal survival and protocol eligibility. Conclusions The identification of key individualized tumor targets in high-risk cancer patients may provide important opportunities for adjuvant therapy with a greater therapeutic index than currently achieved. Close surgical-pathological-oncologic collaboration using established techniques will be important for successful tumor harvest and eventual implementation of a targeted molecular strategy.

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Mir 21 Expression Patterns in Mucinous Neoplasms of the Pancreas M. Dillhoff,* W. Frankel, S. Wojcik, C. Croce, M. Bloomston. *Surgical Oncology, Ohio State University, Columbus, OH.*

Introduction: MicroRNAs (miRs) are small (~22nt) RNA fragments which function by inhibiting the translation of other genes. We have shown that miR-21, which is known to be important in various cancers, is differentially upregulated in human pancreatic adenocarcinomas. We sought to determine if miR-21 expression is also increased in mucinous neoplasms of the pancreas. Methods: Specimens from 26 patients undergoing pancreatectomy for intraductal mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) of the pancreas were microdissected. RNA was extracted and miR-21 levels determined by stem-loop quantitative RT-PCR. Samples were normalized to the small nuclear RNA U6. Results: Samples compared consisted of 19 IPMNs (6 adenomas, 3 borderline, 10 invasive) and 7 MCNs (4 adenomas, 2 borderline, 1 invasive). In the 10 patients with invasive IPMNs, samples were also obtained from the associated invasive cancer. No significant differences in miR-21 expression were seen in invasive vs. non-invasive mucinous neoplasms ($p=0.577$), in invasive neoplasms vs. associated cancer ($p=0.13$), or in non-invasive neoplasms vs. cancers arising from mucinous neoplasms ($p=0.12$). Conclusions: Although miR-21 is known to be overexpressed in established pancreatic cancers, it is not significantly altered in pancreatic cancer precursor lesions (i.e. mucinous neoplasms) compared to associated pancreatic cancers. Our data suggest that alterations in miR-21 expression in pancreatic cancer may be a late event and not involved in its initiation. Global gene expression patterns in mucinous neoplasms of the pancreas may provide insight into the development of pancreatic cancer.

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Mir 21 Expression by In Situ Hybridization in Periampullary Pancreatic Neoplasms M. Dillhoff,* W. Frankel, C. Croce, M. Bloomston. *Surgical Oncology, Ohio State University, Columbus, OH.*

Introduction: We have shown that microRNA(miR)-21 is differentially overexpressed in pancreatic cancers relative to normal adjacent pancreas and chronic pancreatitis. We sought to correlate these findings with miR-21 expression by in situ hybridization as well as to determine its expression in cancers of the ampulla of Vater. Methods: Tissue microarrays were constructed from 30 resected pancreatic cancers, 18 ampullary cancers, 16 chronic pancreatitis specimens, and 10 normal pancreas specimens. RNA was also extracted from the 30 pancreatic cancer specimens and adjacent normal pancreas and hybridized to a microRNA microarray chip. In situ hybridization was undertaken on the tissue microarrays using locked nucleic acid probes. Nuclear RNA U6 served as positive control. Results: Increased miR-21 expression was seen in 27/30 (90%) pancreatic cancer samples relative to adjacent normal pancreas by microarray. MiR-21 was similarly expressed in 29/30 (97%) samples by in situ hybridization compared to 1/10 (10%) normal pancreas and 3/16 (19%) chronic pancreatitis specimens ($p<0.001$). MiR-21 was expressed in 10/18 (56%) ampullary cancers ($p=0.04$ vs. normal pancreas). In all cancer specimens, miR-21 expression was seen only in tumor cells and not in the surrounding stroma. Conclusions: In situ hybridization accurately reflects the expression patterns of miR-21 in pancreatic cancer as determined by microarray analysis. Utilizing this methodology, we have shown that increased miR-21 expression is also seen in cancers of the ampulla of Vater, albeit to a lesser degree.

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Gene expression profiling predicts the therapeutic response of basal-like breast cancers to neoadjuvant chemotherapy Y. Lin,[1]* S. Lin,[2] M. Watson,[1] K. Trinkaus,[1] T. Fleming,[1] K. Weilbaecher,[1] M. Naughton,[1] R. Aft.[1] *1. Surgery, Washington University, St. Louis, MO; 2. University of Pennsylvania, Philadenphia, PA.*

Neoadjuvant chemotherapy allows local tumor response to be used as a surrogate for treatment effectiveness. Gene signatures predicting response to various treatment regimens have been published. These studies considered breast cancer as a homogeneous entity, although higher rates of pathologic complete response (pCR) to neoadjuvant chemotherapy are achieved within the basal-like group. We postulated that unique gene expression profiles exist within the basal-like tumors which predict chemotherapy response. Methods: The "intrinsic" gene expression signature (Perou et. al, Nature 406:747) was used to differentiate breast cancer subclasses. 54 basal-like tumors were identified from two independent neoadjuvant therapy gene expression profiling studies. 28 data sets were from a study at our institution using needle core biopsies from 120 patients. 26 additional data sets were identified from a published study performed on fine needle aspirates (Hess et al., JCO 24:4236). All samples were partitioned chronologically to form a 42 sample training group with 12 samples sequestered for validation. Clinical surveillance occurred for a mean of 26 months post-therapy. Results: An adjusted t-statistic with linear discrimination analysis identified a 77-probe sets which distinguished patients with pCR from those with residual disease (RD). This signature achieved 92% predictive accuracy on the sequestered data. Unsupervised clustering of the entire data set with this signature yielded the expected partitions of tumors with pCR versus RD. Additionally, a small, distinct subset of patients with higher rates of cancer recurrence was observed within this clustering, even though the discrimination model was not formulated to address recurrence. Disease-free survival (DFS) analysis revealed no significant difference in DFS between the pCR and RD subsets. However, patients in the third subset exhibited reduced DFS ($p<0.009$). Conclusions: We identified a 77-probe sets signature which predicts response of basal-like breast cancers to neoadjuvant chemotherapy as well as DFS. This signature is independent of tissue collection method and chemotherapeutic regimen.

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Does Hormonal Receptor Status Concordance of Metachronous Breast Cancers Impact Survival? S.L. Chen,* S.R. Martinez. *University of California: Davis Medical Center, Sacramento, CA.*

Introduction: Hormonal receptor status is an important prognostic factor in breast cancer. It is unclear whether the estrogen receptor (ER) status of the initial breast cancer influences survival after recurrence. We hypothesized that patients with metachronous breast cancers would have a higher incidence of hormonal receptor concordance with their first breast cancer than expected and that this concordance would have an impact on survival. Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for all patients diagnosed with at least 2 breast cancers separated in time, with the first cancer occurring between 1988 and 2004. Patient demographics (age, gender), tumor staging (size, extent, nodal status, metastastic status), tumor characteristics (grade, ER), and initial tumor hormonal receptor status were recorded. Patients were excluded for incomplete data. Chi square and Cox regression starting at the diagnosis of the 2nd cancer were used as appropriate. Results: Study criteria were met in 5,466 patients. Of first cancers, 74.4% were ER positive. The receptor status concordance rates for patients originally ER positive was 82.7%. For those originally ER negative: 55.4%. This demonstrated a significant correlation ($p<0.001$). On multivariate analysis for survival, however concordance in ER status was not a significant predictor of survival ($p= 0.12$). Original ER status was also not a significant prognostic factor ($p=0.07$). Factors that positively impacted survival were younger age, lower T-stage, lower N-stage, recurrent tumor positive ER status, and lower grade. Conclusions: Metachronous breast cancers are more likely to exhibit a similar hormonal receptor profile to the index breast cancer. Hormonal receptor concordance and the initial tumor ER status do not have significant independent impact on survival separate from the recurrent tumor's ER status.

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Validation of a nomogram to predict the risk of non-sentinel lymph node metastasis in breast cancer patients with a positive sentinel node biopsy R.F. Van la Parra,[1]* M.F. Ernst,[1] J.M. Broekman,[2] P.C. Barneveld,[3] K. Bosscha.[1] *1. Surgery, Jeroen Bosch Ziekenhuis, 's Hertogenbosch, Netherlands; 2. Pathology, Jeroen Bosch Ziekenhuis, 's Hertogenbosch, Netherlands; 3. Nuclear medicine, Jeroen Bosch Ziekenhuis, 's Hertogenbosch, Netherlands.*

Background: Completion axillary lymph node dissection (ALND) remains, according to the Dutch guidelines, the standard of care for patients with a positive sentinel lymph node. However, approximately 40-60% of patients with positive SLNs will have no additional positive nodes. To identify the individual patient's risk for non-SLN metastases, the Memorial Sloan-Kettering Cancer Center (MSKCC) developed a nomogram currently available as an online tool. The purpose of this study was to validate the nomogram in a Dutch population of breast cancer patients. Materials and methods: The medical records of 193 breast cancer patients who underwent sentinel lymph node biopsy examination and ALND were selected from a prospectively collected database and were reviewed for multiple clinicopathologic variables. A receiver operating characteristic curve was drawn and the area under the curve was calculated to assess the discriminative power of the nomogram. Also, data of the index and test populations were compared. Results: The area under the ROC curve was .693 (range .614- .773), as compared to .76 in the MSKCC study. When the tool was applied solely to macrometastases, the area under the ROC was .688 (range .595- .781). Conclusions: The MSKCC-nomogram seems to be a useful tool to predict the individual patients risk for positive axillary non-sentinel lymph nodes in a Dutch population of breast cancer patients. Further analysis, however, has to be performed to identify subgroups, in which the nomogram is even more predictive. Predicting the risk of additional nodal metastases will allow the surgeon and patient to make an individualized decision regarding the need for completion axillary lymph node dissection. Key Words: axillary metastases- breast cancer- nomogram- prediction- sentinel node.

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Pre-operative needle biopsy and surgical evaluation of the axilla as quality measures in breast cancer surgery B.J. Pocock,* B. Taback, L. Klein, K.A. Joseph, M. El-Tamer. *Breast Surgery, Columbia Presbyterian Medical Center, New York, NY.*

Introduction: Pre-operative needle diagnosis (PND) of cancer and axillary node procedure (ANP) are being considered as quality measures in breast cancer surgery. These criteria have not been evaluated in the literature. The purpose of this study is to assess the ease of access of these data and their rate of compliance in a tertiary care center. Methods: We retrospectively reviewed all our breast cancer cases between 2006 and 2007. The data were queried for PND and surgical ANP. The charts of patients who did not meet these criteria were reviewed to determine the cause for non-compliance. Results: In the year 2006-2007, 396 breast cancer operations were performed (age range 19-96). PND of cancer was missing in 43/396 (11%) cases. In 19/396 (5%) cases PND was not feasible due to technical reasons. In 22/396 (5.5%) cases, the pre-operative needle biopsy did not render a malignant diagnosis such that the pathology report was discordant with the radiological or clinical findings, or the needle biopsy result necessitated surgical resection. In only 2/396 cases (0.5%) PND was not attempted: 1. an 80 year old woman with a radiologically and clinically malignant mass, and 2. a 43 year old woman with a clinical and ultrasonographic suggestion of fibroadenoma. Surgical ANP was omitted in 17/396 cases (age range 70-95; median 80). All patients had clinically negative axillae with either estrogen and/or progesterone receptor positivity. In all 17 cases, the ANP were omitted due to associated medical conditions. Of note, 34/379 (9%) patients who underwent a surgical ANP were 70+ years old. Conclusions: Data on PND and ANP are easily accessible. If these two criteria are used as quality measures in breast cancer surgery, 100% compliance may not be an achievable goal.

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Margin Width Correlates with Residual Disease at Re-Excision for Ductal Carcinoma in Situ of the Breast R.M. Fearmonti,* L.I. Batista, F. Meric-Bernstam, K.K. Hunt, I. Bedrosian, H.M. Kuerer, S.E. Singletary, G.V. Babiera. *Surgical Oncology, M.D Anderson Cancer Center, Houston, TX.*

BACKGROUND: Surgical margin status is one of the most important risk factors for local recurrence in ductal carcinoma in situ (DCIS) of the breast. What defines an adequate margin width (MW) for DCIS remains a subject of debate and impacts the decision to reoperate for margin control. We evaluated the association of MW and other clinicopathologic factors with the finding of residual DCIS (RD) upon re-excision (RE). METHODS: A prospectively maintained database identified 383 women with DCIS initially diagnosed by core needle or excisional biopsy who were planned for breast conserving therapy and underwent RE at our institution from April 1996 to December 2005. Patients with concomitant ipsilateral invasive (n=116) or bilateral (n=56) breast cancers, and those who did not undergo RE or with unknown MW (n=33) were excluded from the study. The study population was composed of 178 patients. MW and the presence of RD upon RE were obtained from pathology reports. Logistic regression techniques and univariate analysis were used to determine the association of MW and clinicopathologic features (age, clinical presentation, grade, and histologic subtype) with the finding of RD on RE. RESULTS: Median patient age was 54 years. The initial mammographic size ranged from 0.1 cm–9 cm. The frequency of finding RD upon RE varied with MW ranging from 0 to >5mm (Table). There was a significantly higher risk of RD for MW<1mm compared to >1mm (OR 4.6, 95% CI 1.8,11.9). MW was also significantly associated with the presence of RD upon RE (p=0.0291) with a 27% reduction in the odds of finding RD (OR 0.73, 95% CI 0.55,0.97) for each millimeter increase in MW. There were no other statistically significant clinicopathologic features associated with RD on RE. CONCLUSION: Our data shows that a MW of <1mm is associated with a 4.6 times higher risk of RD compared with MW>1mm. A MW of 1 mm or less does not ensure complete removal of disease and was associated with at least a 50% frequency of finding RD at reoperation in our patient population. Long-term followup is needed to assess the clinical relevance of MW on locoregional recurrence.

Table. Frequency of Finding RD on RE

Margin Width (mm)	RD, #patients (%)	Frequency RD
0	69 (38.8)	70.4%
0< MW<1	5 (2.81)	62.5%
MW = 1	24 (13.5)	50.0%
1< MW<2	5 (2.81)	29.4%
2< MW<5	1 (0.56)	33.3%
MW >5	2 (1.12)	50.0%

RD=residual disease, RE=re-excision

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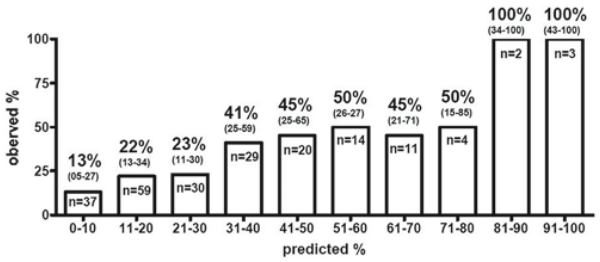
Analysis of clinical applicability of the Breast Cancer Nomogram for positive sentinel lymph node: the Canadian experience E. Poirier,[1]* L. Sideris,[2] P. Dubé,[2] P. Drolet,[2] S. Meterissian.[1] *1. Surgical Oncology, McGill University Health Center, Montreal, QC, Canada; 2. Maisonneuve-Rosemont Hospital, Affiliated Center-University of Montreal, Montreal, QC, Canada.*

Introduction: Completion axillary dissection is sometimes controversial after a positive sentinel lymph node (SLN). A model for predicting non-sentinel lymph node (NSLN) involvement has been developed and prospectively tested in several series. However, its clinical applicability has never been tested among surgeons. Methods: The Breast Cancer Nomogram (BCN) developed by the Memorial Sloan-Kettering Cancer Center was applied to a consecutive series of 209 SLN-positive patients. The performance of the BCN was assessed by the area under the receiver operating characteristic (ROC) curve. Surgeons in Quebec were surveyed to determine the predicted NSLN positivity below which they would not dissect the axilla. The accuracy of the BCN was determined in this clinically relevant range. Results: The predictive accuracy of the BCN had an area under the ROC curve of 0.69, matching other reported series. More than half of interviewed surgeons treat over 20 breast cancer patients per year. Thirteen out of 75 surgeons questioned would never leave the patient without a completion axillary dissection after a positive SLN, regardless of the BCN result, while seventy two percent of them would not complete axillary dissection if the prediction of a positive NSLN was 10% or less. However, only 37 of the 209 (18%) patients were in this 10% or less category, with a mean observed rate of positive NSLN of 13% (95% CI, 5-27%). The false

negative rate among these 37 patients was 14%. Conclusions: The BCN performed fairly well in the whole cohort of patients. Prediction of a positive NSLN must be 10% or less to be clinically applicable and acceptable by the majority of our surgeons. Although useful, the BCN data should be used with caution at the low end of the scale. Because of some limitations in the performance in this category, other clinical factors and judgment must accompany its use.



Relationship between observed percentages of NSLN metastasis vs predicted percentages by the Breast Cancer Nomogram. 95% Confidence Intervals are indicated below the observed percentages.

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Breast cancer risk factors in younger and older women J. Chun,[1]* B.J. Pocock,[1] K. Joseph,[1] L. Klein,[1] M. El-Tamer,[1] F.R. Schnabel.[2] *1. Surgery, Columbia University Medical Center, New York, NY; 2. New York University Medical Center, New York, NY.*

Introduction: Information is lacking regarding the interaction of established breast cancer risk factors and patient age. We attempted to study this interaction in high-risk women at the extremes of age in our population. Methods: The Women At Risk Registry was queried for women who were ≤35 and ≥70 years of age. Enrollment criteria for this program included: strong family history of breast cancer (FHBC), and/or biopsy-proven history of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), or lobular carcinoma in situ (LCIS). Descriptive analyses and Fisher's exact tests were used to analyze these factors over time and to assess their influence on breast cancer development. Results: The total population included 1412 high-risk women with a median follow-up of 4 years. Of 195 women ≤35 years of age (range 20-35 years), 3 (1.5%) developed breast cancer. All 3 cases had a strong FHBC and none had a prior high-risk lesion. Of 82 women ≥70 years of age (range 70-91 years), 6 (7.3%) developed breast cancer. The Fisher's tests demonstrated that ADH (p=0.15), ALH (p=1.0), LCIS (p=1.0), and FHBC (p=1.0) were not associated with breast cancer development in older women. The mean Gail score for women ≥70 years was 4.3, as compared to 4.7 in the subset of older women diagnosed with cancer. The Gail score is not validated for women ≤35 years of age. Conclusions: Our results indicate that in women ≤35 years of age, a strong FHBC may be a more important predictor for breast cancer development than high risk lesions. For women ≥70 years of age, FHBC and history of ADH, ALH, and LCIS were not strong predictors of breast cancer development. Recommendations for risk management in older high risk women may be the same as the baseline population, since age remains the only important risk factor in this group. This study emphasizes the importance of defining age-appropriate recommendations for breast cancer risk management, including surveillance and chemoprevention. Further studies are needed to define appropriate management strategies for very young women at high risk to develop breast cancer.

Distribution of Risk Factors

Risk Factor	Patients ≤35 years (N=195)	Patients ≥70 years (N=82)
FHBC	176 (90%)	52 (63%)
LCIS	12 (6%)	27 (33%)
ADH	20 (10%)	20 (24%)
ALH	5 (3%)	5 (6%)

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Intra-operative ultrasound as the preferred method of localization for nonpalpable ductal carcinoma in-situ M.R. Hart, L.E. McCahill,* T.A. James, R. Single, C. Gaspari. *Department of Surgery, University of Vermont, Burlington, VT.*

Background: The purpose of this study was to determine whether intra-operative ultrasound vs. mammographic needle localization (MNL) is more effective in achieving adequate margins in (nonpalpable) ductal carcinoma in-situ (DCIS). Our objective was also to evaluate the efficacy of both procedures with respect to cost and convenience. Methods: Data was collected from a four-year, prospective Breast Cancer Surgical Quality Database. All DCIS cases were identified and the margin status was compared between those who underwent partial mastectomy (PM) by surgeon intraoperative ultrasound localization (Group 1), and those who underwent PM by MNL (Group 2). Ultrasound localization involved identification of clips placed at stereotactic biopsy, hematoma, or biopsy cavity. Re-excision rates were determined for both groups. The average cost of each procedure was also determined using institutional financial records. Results: A total of 123 patients undergoing PM for non-palpable DCIS were identified from the database. In the 68 patients undergoing ultrasound-guided PM (Group 1), the positive margin rate was 11.8%, and close margins (<1mm) were observed in 22.1% after initial surgery. Fifty-five patients underwent MNL (Group 2); the positive margin rate was 14.5% and close margins were observed in 20.0%. The difference between positive and close margins in Group 1 versus Group 2 was not statistically significant (p=NS, Fisher's exact test). The rate of re-excision was 27.9% for Group 1 and 32.7% for Group 2, resulting in 1.28 and 1.42 operations per patient, respectively (p=NS, Fisher's exact test). It was determined that the average cost of an intra-operative ultrasound at our institution was $933 and $1,858 for MNL (excluding cost of radiologic interpretation), a difference of $925 per case. Conclusion: Our study showed equivalent rates of positive margins and re-excision between intra-operative ultrasound and MNL when performing lumpectomy for non-palpable DCIS. Considering the more invasive nature and increased cost of MNL; we consider intra-operative ultrasound, when possible, the more cost effective and practical procedure for patients with nonpalpable DCIS.

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Treatment of Breast Cancer in Maine P. Teller,* M. Feinberg, M. Schwemm MD, C. Verrill MPH, L. Rutstein MD. *General Surgery, Maine Medical Center, Portland, ME.*

Objective: Analyze concordance with national guidelines for breast cancer treatment in Maine. Identify areas for quality improvement. Propose a model to apply to other tumor sites. Methods: The Maine Cancer Treatment Workgroup comprised of oncologists, hospital registrars, ACS and registry staff performed a retrospective analysis of data from 2002-2004. Comparisons to national benchmark were conducted per ACoS/CoC standards. Results: Data analysis included: breast conservation rate, post-lumpectomy radiation delivery, sentinel lymph node biopsy (SLNB) rate and hormone therapy use. Data were investigated over time, stage, age and geographic regions. The lumpectomy rate over all stages was 58%; national benchmark is 65%. Maine exceeded benchmark lumpectomy rate in Stage 0 and I disease at 68% and 72%. Lumpectomy rates decreased over 3 years from 61% to 55%. The majority of patients under age 40 underwent mastectomy. Geographic differences in lumpectomy rate were observed. The Northeast region had a statistically lower lumpectomy rate. Considering post-lumpectomy radiation, national benchmark was 95% for Stage 0 and 100% for Stages ≥I. Post-lumpectomy radiation rates were lower at 60%, 83% and 78% for Stages 0, I and II. Statistical differences existed in the post-lumpectomy radiation delivery rate between Northeast and other regions. Benchmark for SLNB in Stage I/II disease is 100%. The statewide SLNB rate was 61% for Stage I and 49% for Stage II disease. An 11% improvement was observed in SLNB over 3 years. There is no available benchmark data for hormone therapy use. After stratifying pre- and post-menopausal groups, the rate of hormone administration remained 65% for receptor positive patients. Conclusions: Data collection and analysis identified areas for statewide improvement in breast conservation therapy, SLNB and post-lumpectomy radiation. Workgroups can be assembled to develop strategies to address each of these deficiencies. This data analysis will improve quality and access to care for all breast cancer patients statewide. The model can be applied to other primary tumors.

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Does the adoption of sentinel node biopsy account for the increase in node positivity in women with T1 tumors? L.K. Helyer,[1]* N.G. Coburn,[3] C.H. Law,[3] D.R. McCready.[2] *1. Surgery, Dalhousie University, Halifax NS., NS, Canada; 2. Princess Margaret Hosptial, Toronto, ON, Canada; 3. Sunnybrook Health Sciences Center, Toronto, ON, Canada.*

Breast cancer micrometastases (N1mic) are deposits of tumor in axillary lymph nodes < 2mm. Sentinel node biopsy (SNB) with its more focused surgery and in depth pathologic analysis, may cause women to be upstaged due to the diagnosis of N1mic. We examined the trends of nodal staging in women with T1 breast cancers using a population approach. Patients and Methods: Data from the Surveillance, Epidemiology, and End Results database (SEER) were analyzed from 1992 to 2003 to determine the status of axillary nodes in women with T1(≤20mm) ductal breast cancer undergoing definitive breast and axillary surgery (n=126475). Univariate and multivariate analysis were used to determine predictors of node positive/N1mic disease including tumor size, grade, breast/axillary surgery type and date of diagnosis. Results: From 1992 to 2003, the rate of node positivity in women with T1 tumors increased from 8 to 15.6% and was found in all size categories (T1a: 2.4 to 6.2%, T1b: 4.4 to 9.9%, T1c: 10.6 to 21.5%). The detection of N1mic disease rose 3-fold (1.8 to 5.8%) coinciding with the increased use of SNB since 1998 and spanned T1a (0 to 2.8%), T1b (1.4 to 4.2%), and T1c (2.4 to 7.0%) stages. Macrometastases (>2mm) also increased in patients with T1a:2.4 to 3.4%, b:3.0 to 5.7% and c:8.2 to 14.4%, found primarily by axillary dissection (ALN)without SNB. On multivariate analysis, the odds ratio (OR) of detecting N1mic disease increased with year of diagnosis compared with 1992, OR of 1.56 in 1995 (p=0.0029) and 2.03 in 2003 (p<0.0001). Patients undergoing SNB had a 2.25 increased rate of finding N1mic compared to an ALN(p<0.0001). Younger age, larger tumor size, and estrogen receptor positivity were significantly associated with N1mic disease but to a lesser degree. Conclusions: Node positive status is more common in 2003 than 1992 in T1 tumors. This is due to an increase in detection of both micro- and macrometastases. The increased detection of N1mic coincides with the adoption of SNB. Increased detection of N1mic disease by ALN suggests there are other reasons for the increase in node positivity rates such as improved surgical and pathological technique.

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Predictors of Residual Disease After Re-Excision for Close Margins in Breast Cancer M.S. Sabel, C. Gajdos,* K.M. Diehl, V.M. Cimmino, A.E. Chang, L.A. Newman. *Surgical Oncology, University of Michigan, Ann Arbor, MI.*

Introduction: While the data is clear that re-excision is necessary for patients with positive margins, there remains debate as to whether a close margin mandates re-excision. We attempted to identify a subset of patients with close margins who had a low incidence of residual disease in the re-excision specimen. Methods: We queried our prospective IRB-approved breast cancer database for all patients who underwent either a re-excision lumpectomy or mastectomy for a close but negative margin (defined as within 2mm) over a 4 year period. Using the presence of residual disease in the re-excised specimen as an endpoint, we attempted to correlate clinical, mammographic and histopathologic features with the presence of residual disease. Univariate analysis was performed using Fisher's exact test. Results: Between Jan 2001 and Dec 2005, 948 patients were taken to the operating room with the intent of performing a lumpectomy for either DCIS or invasive cancer. 304 patients (32%) required additional surgery, 173 (18%) for a positive margin and 131 (14%) for a close margin. Of these 131 patients, residual disease was identified in 43 (33%) patients. Residual disease was more common in patients with DCIS than invasive cancer (44% vs. 29%, p=NS). For 32 DCIS patients with close margins, nearly all the patients presented similarly, with calcifications on mammogram (29 of 32) diagnosed by stereotactic core biopsy (25 of 32). Neither tumor size, location nor grade was associated with the presence of residual disease. Of the patients with invasive cancer, only multifocality was significantly associated with residual disease (52% vs. 23%, p=.025). Presentation, mammographic findings, type of biopsy, tumor size, grade, histology, ER/PR status nor an extensive intraductal component was significantly associated with residual disease. Conclusion: Residual disease is left behind in the breast in nearly 1/3 of lumpectomies with negative margins <2mm. It is not possible to satisfactorily stratify risk to consider avoiding re-excision. Re-excision should be performed for all margins less than 2mm for both DCIS and invasive cancer.

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DNA Methylation as a Biomarker for Breast Cancer Risk G. Zapparoli,[2] R. Sullivan,[2] S. Kim,[2] J. Cangiarella,[2] K.A. Skinner.[1]* *1. Surgery, University of Rochester School of Medicine and Dentistry, Rochester, NY; 2. NYU School of Medicine, New York, NY.*

Atypical ductal and lobular neoplasias(AN, including atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ) are among the major risk factors for breast cancer(BC), yet the majority of women diagnosed with AN do not develop BC. The purpose of this study was to determine whether DNA methylation patterns could be used to predict which women with AN would go on to develop BC. Methods: 35 patients who had biopsy proven AN and at least 5 years of followup were identified through pathology archives and medical records, and blocks from the biopsies showing AN were obtained. Two 10 micron sections were cut and DNA was extracted and bisulfite converted. MethyLight assay was used to determine the methylation status of 8 tumor suppressor genes (APC, CALCA, CyclinD2, GSTP1, HPP1, MyoD1, RARB2, and RassF1).Results: Of the 35 patients, 23 developed subsequent cancer (ANCA) with a mean time to cancer of 54 months (range 7-118) and 12 did not develop cancer (ANNoCA) at a mean followup of 120 months (range 60-178). Methylation data is shown in Table 1. ANCA samples were hypermethylated compared to ANNoCA at CALCA and APC, and hypomethylated compared to ANNoCA at MyoD1 (p<0.05), with a trend toward hypermethylation at RARB2 and HPP1 (p=0.08). The average number of methylated genes per sample (NMG) was significantly higher in ANCA samples. By weighting the contribution to the NMG for each gene by the difference between the % of samples methylated in ANCA vs in ANNoCA, a weighted score (WNMG) is obtained. The average WNMG for ANCA is significantly higher than that for ANNoCA (1.24 vs -0.3, p<0.0001). The WNMG score can distinguish between ANCA and ANNoCA with a sensitivity of 100%, specificity of 58%, positive predictive value of 82%, and negative predictive value of 100%. Conclusions: DNA methylation patterns in AN biopsies can distinguish between patients who do and do not subsequently develop breast cancer. A prospective study will be needed to validate these results and determine their clinical utility.

Table 1: % of Samples Methylated

Gene	GSTP1	CALCA	RARB2	APC	MYOD1	CYCD2	HPP1	RASSF1	NMG
ANCA (n=23)	9%	26%	22%	39%	9%	17%	21%	91%	2.3
ANNoCA (n=12)	0%	0%	0%	8%	58%	0%	0%	100%	1.7
P-value	0.129	0.05	0.08	0.05	0.001	0.12	0.08	0.29	0.04

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Rate of Re-excision with Breast Conserving Therapy With and Without Additional Margins in patients with Ductal Carcinoma in Situ Y.H. Wen,[1] D.F. Roses,[2] D.M. Axelrod,[2] A.A. Guth,[2] R.L. Shapiro,[2] R. Berman,[2] B. Singh.[1]* *1. New York University Department of Pathology, New York, NY; 2. New York University Deparment of Surgery, New York, NY.*

Background: Margin distance is a significant predictor of residual disease and local recurrence in patients with DCIS. This study aims to correlate rate of re-excision with breast conserving therapy with and without concurrent additional margin excision. Design: Patients who underwent surgery at NYUMC for DCIS between January 2004 and July 2007 were identified and pathology reports were reviewed. Results: 405 patients who underwent surgery for DCIS were identified. Mean age at diagnosis was 58 years (range, 29-98 years).Table 1 shows clinicopathological characteristics of the patients, treatment strategies, DCIS extent, grade, the presence or absence of necrosis, and the rates of re-excision and residual disease. Of the total 405 patients, 201 (50%) were treated with breast conservative surgery without additional margins (BCS), 151 (37%) were treated with BCS with additional margins (BCSAM), and 53 (13%) with total mastectomy (TM). Margins were positive for DCIS in 43 (21%) of 201 patients treated with BCS, and in 17 (11%) of 151 patients treated with BCSAM (P<0.05); margins were widely negative (> 10 mm) in 36 (8%) of 201 patients with BCS, and in 60 (40%) of 151 patients with BCSAM (P<0.0001). Re-excision for close or involved margins was performed in 129 (64%) treated with BCS, and in 61 (40%) treated with BCSAM (P<0.0001). Re-excision was performed in 191 (47%) of the total 405 patients. In those who underwent re-excision, 98 (51%) patients had residual disease (Table 2). 65 (32%) and 33

(22%) (P<0.05) of patients treated with BCS and BCSAM, respectively, had residual DCIS. DCIS-margin distance less than 1 mm was associated with residual disease (P<0.05). The number of margins involved was also associated with residual disease on re-excision, with significantly higher rates when 4 or more close margins present at the original surgery (P<0.01). Conclusion: In this cohort of patients with DCIS, the rate of positive margins, re-excision and residual disease was significantly higher in patients who underwent BCS alone as compared to BCS with additional margins.

Table 1

		BCS	BCSAM	TM
No of patients (%)		201 (50%)	151 (37%)	53 (13%)
Age (mean)		58	59	54
DCIS grade	I	17 (8%)	10 (7%)	5 (9%)
	II	88 (44%)	53 (35%)	15 (28%)
	III	96 (48%)	88 (58%)	33 (62%)
DCIS size (cm)	< 1	67 (33%)	44 (29%)	9 (17%)
	1-2	37 (18%)	22 (15%)	6 (11%)
	2-5	27 (13%)	19 (13%)	9 (17%)
	>5	9 (4%)	1 (1%)	2 (4%)
	N/A	61 (30%)	65 (43%)	27 (51%)
Necrosis	Yes	124 (62%)	106 (70%)	40 (75%)
	No	77 (38%)	45 (30%)	13 (25%)
Margin distance (mm)	Positive	43 (21%)	17 (11%)*	0
	< 1	73 (36%)	44 (29%)	1 (2%)
	1-2	23 (11%)	9 (6%)	0
	3-5	20 (10%)	17 (11%)	0
	6-9	6 (3%)	4 (3%)	0
	>10	36 (8%)	60 (40%)**	52 (98%)
Re-excision		129 (64%)	61 (40%)**	2 (4%)
Residual DCIS		65 (32%)	33 (22%)*	0

*P<0.05 **P<0.001 (BCS vs BCSAM)

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Breast cancer (BCa) patients vaccinated with a MHC Class I peptide (GP2) derived from the transmembrane region of HER2/neu demonstrate intra-antigenic epitope spreading J. Gates,[1]* L.C. Hird,[1] J.P. Holmes,[2] E.A. Mittendorf,[3] M.G. Carmichael,[2] S. Ponniah,[2] G.E. Peoples.[1] *1. Cancer Vaccine Development Program, Department of Surgery, Brooke Army Medical Center, Ft. Sam Houston, TX; 2. Cancer Vaccine Development Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD; 3. Department of Surgery, U.T.M.D. Anderson Cancer Center, Houston, TX.*

Background: BCa patients vaccinated with a peptide (E75) from the extracellular domain of HER2/neu develop intra-antigenic epitope spreading against GP2, a peptide from the transmembrane domain. Here we examine epitope spreading in node-negative (NN) BCa patients vaccinated with GP2. Methods: Following standard therapy, HLA-A2+, NN BCa patients were vaccinated monthly x6 with GP2+GM-CSF in a phase I dose-escalation safety study. E75 and GP2-specific CD8 T cells in peripheral blood samples were measured with HLA-A2:IgG dimer assay using flow cytometry. Antigen-specific CD8 T-cell levels were correlated with standard clinical pathologic features of the patients' tumor. Results: 12 patients have been vaccinated. 6 (50%) had pre-existing immunity (dimer >0.3% pre-vaccine) to GP2 and 4 (33%) had pre-existing immunity to E75. Median GP2-specific CD8+T-cells (GP2-CD8) increased in all patients with pre-vaccine levels (0.27%, range 0-2.0%) versus max post-vaccine levels (0.88%, 0.44-2.93%, p=0.02). E75-specific CD8 T cells (E75-CD8) increased pre-vaccine (0.85%, range 0-2.41%) to max post-vaccine response (1.37%, 0.86-3.57%, p=0.02). Patients without pre-existing immunity to E75 (dimer <0.3%, n=4) had a significant increase in E75-CD8 from pre-vaccine (0.05%, 0-0.25%) compared to max post-vaccine response (1.53%, 0.86-3.57%, p=0.03) and average post-vaccine response (0.41%, 0.38-1.17%, p =0.03). Standard pathologic features of patients' tumor did not impact pre-vaccine dimer levels of GP2 or E75 or response to vaccine. Interestingly, 3 patients who lacked pre-existing immunity to both peptides had 1+ HER2/neu expression via standard IHC, compared to 0/9 patients who had higher levels of HER2/neu and pre-existing immunity to at least 1 peptide (p=0.005). Discussion: Levels of GP2-CD8 increased in patients vaccinated with GP2 and all patients also demonstrated epitope spreading to E75. Patients who lacked pre-existing immunity to both peptides had the lowest level of HER2/neu expression. A combination of GP2 and E75 could potentially be a highly effective vaccine for the immunotherapy of BCa.

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Pathologic and immunologic patterns among breast cancer (BCa) patients with clinical recurrence after vaccination with a preventive HER2/neu peptide vaccine (E75) L.C. Benavides,[1]* J.D. Gates,[1] A. Amin,[2] J.P. Holmes,[2] M.G. Carmichael,[2] M.T. Hueman,[2] D. Craig,[3] A. Stojadinovic,[4] S. Ponniah,[2] G.E. Peoples.[1] *1. Cancer Vaccine Development Program, Department of Surgery, Brooke Army Medical Center, Ft. Sam Houston, TX; 2. Cancer Vaccine Development Program, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD; 3. Joyce Murtha Breast Care Center, Windber, PA; 4. Department of Surgery, Walter Reed Army Medical Center, Washington, DC.*

Introduction: Although E75 vaccination of disease-free node-positive (NP) and node-negative (NN) BCa patients appears to reduce the recurrence rate compared to a control group, recurrences have occurred in both groups. We have assessed these recurrences for prognostic factors and immune response to the vaccine. Methods: 180 BCa patients (93 NP, 87 NN) have been enrolled. HLA-A2+ patients (47 NP, 50 NN) were vaccinated while HLA-A2- patients (46 NP, 37 NN) were followed prospectively as controls. Standard prognostic factors were collected. Peripheral blood E75-specific CD8 T-cells (E75-CD8) were measured by flow cytometry using the HLA-A2:Ig dimer assay and in vivo DTH reactions were recorded. Results: At median of 24 months follow-up, there have been no recurrences among the 50 vaccinated NN patients. Among the 47 vaccinated NP patients, there have been 7 recurrences. Comparing these 7 vaccinated recurrences (VR) to the 40 non-recurrent NP patients (NR), the VR group had a higher % of patients with ≥T2 tumors (71% vs. 45%, P<0.2), ≥4+ nodes (86% vs. 13%, P<0.001), high grade (100% vs. 46%, P<0.025), ER-/PR- (57% vs. 25%, P<0.1), and HER2/neu 3+ (29% vs. 20%, P<NS). The VR group had equivalent E75-CD8 to the NR group at baseline, max response and post-response (0.75% vs. 0.8%, 2.41% vs. 1.76%, 0.9% vs. 0.92%). Similarly, the post-DTH was not different between the VR and NR groups (13.6mm vs. 16.2mm). There were 12 recurrences in the control groups (CR). When the 7 VR were compared to the 12 CR, the VR patients had a higher % of patients with ≥T2 tumors (71% vs. 67%, P<NS), ≥4+ nodes (86% vs. 67%, P<NS), high grade (100% vs. 42%, P<0.02), ER-/PR- (43% vs. 17%, P<0.06), and HER2/neu 3+ (29% vs. 17%, P<NS). Conclusions: E75 vaccinated NP patients who recurred had worse prognostic factors compared to non-recurrent patients despite both groups having similar immune responses to the vaccine. When compared to the control patients who recurred, the vaccinated patients appear to have worse prognostic factors suggesting that the vaccine may be preventing recurrences in patients with less aggressive tumors.

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Quality of life in breast cancer patients in Chile A. Leon,* M.F. Ayala, M. Camus, F. Dominguez, B. Nervi, M. Alvarez, M. Contreras, C. Baeza. *Pontificia Universidad Catolica de Chile, Santiago, Chile.*

In Chile approximately 1800 new cases of breast cancer are diagnosed every year, but there are no established protocols that measure direct or indirectly quality of life (QOL) in these patients. Breast cancer and its subsequent treatment has significant impact on the woman's physical and mental health and her well-being, and thereby cause substantial disruption of QOL. The objectives of this study were to evaluate QOL and identify its associated factors in different stages of treatment. Methods: A cross-sectional study was performed including 192 breast cancer patients, who had undergone different oncologic treatments. Sociodemographic, clinical and psycological aspects of their life were evaluated. QOL was rated by Breast Cancer Patient questionnaire. Medical and Psycological outcomes, previously adapted to Chilean women, were measured. This questionnaire, focuses on loss of attractiveness, fatigue, physical symptoms, inconvenience, emotional distress, and feelings of hope and

support from others. Generalized linear models were used to analyze the data, allowing the identification of factors affecting QOL, adjusting for confounding variables. Results: For the groups in stages I and II v/s stage III and IV, there was a negative media difference in psychological well-being. A significant relation was detected between the amount of received treatments and the months from the diagnosis, as well as with the breast cancer stage and the amount of chemotherapy cycles received. No differences were found when comparing partial mastectomy with radical surgery, but in patients younger than 45 years the axillary dissection influenced negatively QOL. Conclusions: Breast cancer with a long active treatment produces significant deterioration of QOL, independent of the applied treatment, socioeconomic status or age. Surgical treatment does not seems to affect the QOL, with the exception of young patients with axillary dissection. Finally, life quality in patients with breast cancer is a reliable and objective index of the efficacy of the treatments carried out.

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The Influence of Opinion Leaders in Areas of Scientific Uncertainty in Breast Cancer A.T. Schroen,* D.R. Brenin. *University of Virginia, Charlottesville, VA.*

Introduction: Medical opinion leaders are known to be influential among their peers in transferring new knowledge into practice. Understanding their relative influence among surgeons may elucidate how influential experts can better serve to raise standards of care in breast cancer therapy across many communities. Our study sought to identify the relative importance of various information sources on surgeons' decision-making in areas of uncertainty in breast cancer. Methods: A survey was mailed in 2005-06 to 2,187 randomly selected members of the American College of Surgeons. A five-point Likert scale was designed to quantify respondents' perceived influence from various information sources on clinical decision-making. These questions specifically addressed decisions on [1] using sentinel lymph node biopsy in ductal carcinoma in situ (DCIS) only, [2] performing completion axillary dissection after a positive sentinel lymph node biopsy, [3] recommending post-lumpectomy radiation for DCIS, and [4] recommending post-mastectomy radiation in patients (pts) with < 4 positive lymph nodes. Responses were analyzed by surgeon gender, practice type, years in practice, oncology training, professional society membership and breast cancer patient volume. Results: 923 responses were received; 460 were eligible for analysis. Respondents included diverse practice types (81% private, 9% academic, 10% other), annual breast cancer volume (40% ≤ 25 pts, 16% >100 pts), additional oncology training (12%), and memberships relevant to breast surgical oncology (9% SSO, 39% ASBS). In all four areas of scientific uncertainty, the opinion of someone regarded as an expert in the field was ranked as the most influential source of information for decision-making (Table 1). Academic surgeons, however, consistently ranked published data as more influential than expert opinion in all four areas of scientific uncertainty. Conclusions: Breast cancer opinion leaders have significant influence on the decision-making of community surgeons when standard practice is uncertain. Opinion leaders should use their influence wisely and responsibly during the evolution of new treatments to improve breast cancer care.

Influence of Information Sources on Surgeons' Decision-making in Areas of Scientific Uncertainty

	Mean Influence of Information Source on a Scale from 1-5 (% responding Not Applicable)						
Area of Uncertainty	Personal Experience	Surgical Training	Expert Opinion	Community Standard of Care	Guidelines or Consensus Statements	Observational Studies	Randomized Control Trial Data
Use of SLNB in DCIS only	2.25 (2%)	3.54 (22%)	**1.80** (0%)	2.89 (6%)	1.97 (5%)	2.10 (3%)	2.30 (23%)
Use of completion ALND after positive SNB	2.30 (1%)	3.06 (22%)	**1.85** (0%)	2.44 (3%)	1.94 (3%)	2.14 (2%)	2.11 (18%)
Use of post-lumpectomy XRT for DCIS	2.26 (1%)	2.61 (11%)	**1.83** (1%)	2.12 (2%)	1.85 (1%)	2.02 (2%)	1.97 (5%)
Use of post-mastectomy XRT for 1-3 positive LNs	2.67 (10%)	3.07 (20%)	**2.0** (9%)	2.46 (11%)	2.08 (11%)	2.25 (10%)	2.20 (16%)

Scores: 1-Strong influence; 3-Some influence; 5-No influence.
Bold score indicates highest mean score for each area of uncertainty.
SLNB-sentinel lymph node biopsy; DCIS-ductal carcinoma in situ; ALND-axillary lymph node dissection; XRT-radiation therapy; LN-lymph node

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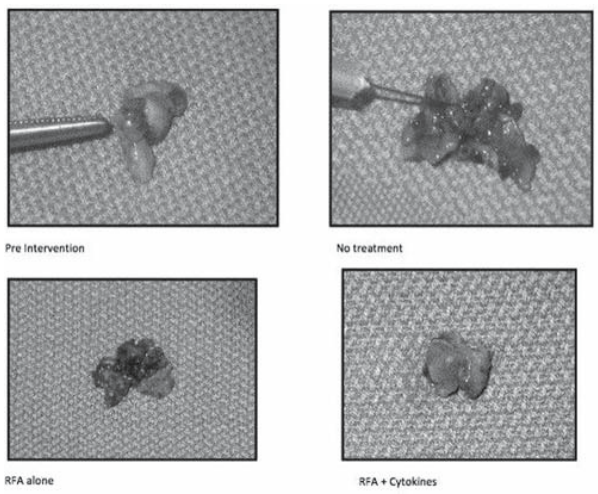
Radiofrequency ablation of breast tumors along with the intralesional administration of IL-7 and IL-15 induce anti-tumor immune responses and inhibit tumor relapse and metastasis M. Habibi,[1]* M. Manjili,[2] H.D. Bear,[2] J.M. Keeler,[2] M. Kmieciak.[2] *1. Surgery, Johns Hopkins University, Baltimore, MD; 2. Virginia Commonwealth University, Richmond, VA.*

Introduction Radiofrequency ablation (RFA) has been used for the treatment of primary tumors. However, tumor relapse or metastasis is always a matter of concern following RFA treatment. RFA has been reported to induce tumor-specific immune responses. However, such immune responses could not always offer protection against tumor recurrence and/or control the metastatic disease. Method To determine whether combination of RFA with immunotherapy may induce tumor-specific immune responses against mammary carcinoma, we evaluated intralesional injection of IL-7 and IL-15 in RFA-treated animals. We used two different breast carcinoma models. The first group, was the 4T1 breast cancer cells inoculated into the flank of Balb/C mice and the second model was the Mouse Mammary Carcinoma cell line inoculated into the flank of FVBN202 transgenic mouse model. There were 40 mice in each groups. Each group were divided into three subgroups of Control (without any treatment), RFA only and RFA plus Intralesional IL7-IL15 (1 mcg each) injection. The tumors were ablated up to 105 degrees Celsius. Tumor recurrence, anti tumor antibodies (Humoral Immunity), Gamma- Interferon release assays (Cell –mediated Immunity), and metastasis to the lung were studied. Results RFA alone failed to induce effective anti-tumor immune responses. However, when combined with the administration of IL-7 and IL-15, RFA was capable of inducing a strong tumor-specific immune responses as well as inhibiting tumor relapse and lung metastasis. After the ablations, the RFA alone group remained tumor free for about 1-2 weeks and then the tumor recurred, where as in the RFA and Cytokine group, the animal remained tumor free. There was a significant increase in the tumor specific antibodies as well as a very potent Gamma-INF response in the RFA-cytokine groups. After 4-5 weeks, there was a significant decrease in the lung metastases in the RFA-Cytokine group. Conclusion: Our observations suggest that combination of RFA with adjuvant immunotherapy using intralesional injection of IL-7 and IL-15 can improve therapeutic efficacy of RFA.



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Is there an optimal skin to catheter distance for balloon catheter brachytherapy in breast cancer? Experiences over five years

E. Schochet,[1]* M.A. Gittleman,[2] S. Eid,[1] J. Matulay,[3] C. Bryk.[2]
1. Department of Surgery, Lehigh Valley Hospital, Allentown, PA; 2. Breast Care Specialists, Allentown, PA; 3. Muhlenberg University, Allentown, PA.

INTRODUCTION: Preliminary data has suggested that balloon catheter brachytherapy (BCB) may be a suitable alternative to whole breast radiation therapy. While a mandatory minimum skin-to-catheter distance (SCD) to minimize toxicity and enhance cosmesis is intuitive, little attention has been given to defining the optimal SCD. METHODS: 208 patients with DCIS and/or invasive T1-T2 breast cancer underwent lumpectomy with nodal sampling and MammoSite catheter insertion by a single surgeon. Computed tomography (CT) was obtained prior to treatment to assess the SCD. Cosmesis and toxicity were recorded at standard intervals. Spearman's correlation and Pearson's Chi-square analysis were used applied. RESULTS: The subjects were 42-90 years old (mean 67.5), and had tumor sizes ranging 0.1 - 2.5 cm (mean 1.00). Follow-up was a mean of 3.1 years (2-69 months) and mean skin distance was 1.1 cm (.04-3.2cm). There was no difference in SCD between the DCIS and invasive groups. At three years follow-up, the mean SCD for those with no toxicity was 1.15 cm and for those with Grade I toxicity was 0.675cm ($p<.001$). When divided into two cohorts of 0.5-1 cm and 1-2 cm, the shallow group had more skin toxicity ($p=.033$) at six months, and at one year, had fewer reports of excellent cosmesis scores (45.2% vs. 71.1%, $p=.005$). Subcutaneous tissue toxicity was more prevalent in the shallow group at one year ($p=.026$), and cosmesis results were slightly better at 6 ($p=.002$), 12 ($p=.005$), and 24 ($p=.012$) months; however the differences disappeared by the three years. CONCLUSIONS: Although it would appear that SCD >1cm results in a better toxicity profile, the acute skin and subcutaneous tissue toxicities were largely grade I and self-limiting. Ultimately, the cosmesis scores were equivalent upon longer follow-up with >90% of patients having good to excellent cosmesis scores at all time points. The psychosocial component of early toxicity in the face of an ultimately acceptable outcome should not be overlooked. It is reasonable to attempt a 1 cm margin however 5-10 mm SCD should still provide a good cosmetic outcome and not preclude full treatment.

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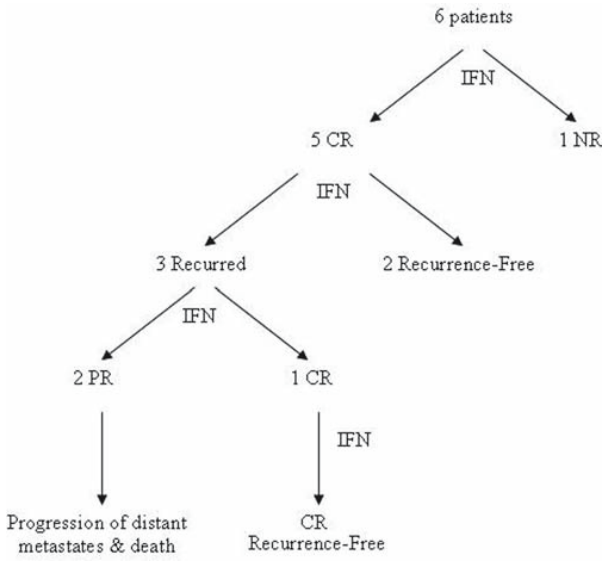
Chronic Management of Unresectable Chest Wall Recurrence with Peritumoral Interferon K.L. Bland, M.A. Smith, R.S. Henry-Tillman, V. Klimberg.* *Surgery, University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: There are few if any effective therapies for unresectable chest wall recurrence in a patient who has already received radiation therapy and progressing on hormonal or chemotherapy. Although systemic interferon (IFN) has demonstrated a poor response in the treatment of metastatic breast cancer, based on preclinical data, we hypothesized that peritumoral IFN would be effective for the treatment of local recurrence when traditional treatment has failed. Methods: Breast cancer patients with unresectable local failure(LF) after mastectomy, radiation, and chemotherapy that were treated with IFN were included. Peritumoral injections of IFN alpha 2b (3-5 million units initially) three times per week or pegylated IFN alpha 2b (pIFN) (0.2-1.0ug/kg) weekly were injected peritumorally around chest wall lesions. Response of LF to treatment was evaluated clinically as complete response (CR), partial (PR) (>50% decrease), or no response (NR). Results: A total of 6 patients with 10 ± 11 lesions were evaluated. Four patients had metastatic disease at the time of presentation. The mean recurrent tumor size was 7.8 ± 6.8 cm. A complete response was observed in 5 patients after 6.8 ± 5.7 injections over 10 ± 12 weeks with a mean duration of this response to treatment of 16.3 weeks (range: 2-43 weeks). (See Figure) Three of the complete responders had a second recurrence treated with 10.3 ± 7.8 injections over 22.7 ± 12.3 weeks. One patient achieved a CR followed by a third LF and again a CR with IFN. Two patients with second LF were able to achieve PR response but because of progression of metastatic disease precluded further treatment with IFN. Three patients died due to progression of systemic disease. The NR, due to metastatic disease, was unable to tolerate even 0.2ug/kg of pIFN. Overall, three patients have remained LF-free for 53 ± 44 weeks(range 20 to 142 weeks). In general greater and quicker regression was seen with increasing doses of IFN. Conclusion: Peritumoral IFN injections of chest wall recurrences may provide an effective therapeutic option for the chronic management of even extensive LF in breast cancer patients.



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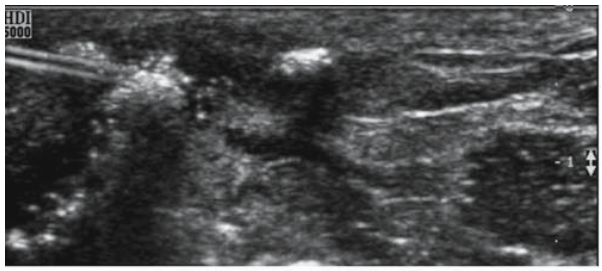
Technical enhancements to breast ductal lavage M. Nejad,[2] J. Tondre,[1] D. Mills,[1] S.M. Love.[1]* *1. Dr. Susan Love Research Foundation, Pacific Palisades, CA; 2. University of California, Los Angeles, CA.*

Introduction: Ductal lavage is a minimally invasive procedure that allows for the sampling of the epithelial lining and fluid from a breast duct for cytomorphology, endogenous hormones and other risk or cancer biomarkers. We present recent advances that should ease concerns over the challenges of duct cannulation, possible perforation, and low participant return rates. Pre-lavage ductoscopy and real time ultrasonography can detect perforations and prevent unintentional analysis of stroma. An intranipple lidocaine injection prior to duct lavage immediately anesthetizes the nipple and flattens out folds to make the ductal orifices more obvious whether they yield fluid or not. Methods: In an ongoing study healthy women consented to undergo nipple aspiration and ductal lavage of 3-4 ducts. Volunteers were given a 1% lidocaine with bicarbonate injection to the nipple before ductal cannulation. An Acueity ductoscope was used prior to catheterization to visualize the anatomy and a high definition ultrasound was used for real time imaging during the lavage procedure. Ultrasonography identified fluid filling branching ducts, perforated ducts and lactiferous sinuses. Fluid samples were collected whether or not the duct was determined to be perforated. Results: To date, lavage has been performed under ductoscopy and ultrasound on 209 definite ducts in 78 women. Of these we found 21 confirmed perforations, and seven with unknown anatomy for a perforation rate of 10%. We had no difficulty identifying at least three ducts per breast. Our volunteers do return for their 6 month study follow-up visit (96%) and 91% reported a 0 (0-10 range) pain score two weeks after the procedure. Conclusions: Confirmation of ductal lavage can be effectively achieved by ductoscopy and sonoductography. We now recommend real time sonoductography as the more valuable tool in establishing the anatomical structure being lavaged. This can easily be performed in the office by surgeons trained in breast echography. We also highly recommend the use of the intranipple lidocaine injection which allows for increased feasibility in finding ducts and lower pain levels resulting in a higher patient return rate.



Perforation- bubbles and pooling of fluid

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Impact of Ultrasound and Clinicopathologic Factors on the Accuracy of Sentinel Lymph Node Dissection in Breast Cancer Patients Following Neoadjuvant Chemotherapy C. Ching,* E.A. Mittendorf, M. Yi, B. Naik, G.V. Babiera, B.W. Feig, M.I. Ross, K.K. Hunt. *Surgical Oncology, MD Anderson Cancer Center, Houston, TX.*

Background: The ability of sentinel lymph node dissection (SLND) to predict axillary nodal status in breast cancer patients after neoadjuvant chemotherapy (NC) has been questioned, with false negative (FN) rates up to 25% reported in patients presenting with node positive (NP) disease. Ultrasound (US) has a reported 75% accuracy in assessing axillary response. This study was performed to evaluate our experience with SLND in NP patients who received NC and to determine the ability of US and clinicopathologic factors to predict SLND accuracy. Methods: Review of our institutional database of 5479 patients undergoing SLND identified 109 patients with NP disease treated with neoadjuvant chemotherapy followed by SLND and completion ALND as part of definitive surgical therapy. Clinicopathologic factors including chemotherapeutic agents, histology, clinical T and N stage before and after therapy and US evaluation of the lymph nodes were recorded. Pathology was reviewed and accuracy and FN rates were calculated. Results: A SLN was successfully identified in 102 (94%) patients and this accurately predicted nodal status in 81 (79%). The FN rate for the entire group was 21%. At completion of neoadjuvant therapy, 97 (95%) of these 102 patients underwent axillary US. In the subgroup of patients with an abnormal US after therapy (n=43), corresponding to persistent disease, the FN rate was 28%. A normal US, corresponding to complete clinical response (CR), was seen in 59 (61%). In this subgroup, the SLN was positive in 25 (43%) and negative in 33 (57%). SLND accurately staged the axilla in 48 (83%), and the FN rate was 17%. No clinicopathologic features were predictive of a FN SLN in these patients (table). Conclusion: These data suggest that US evaluation may be useful in increasing the sensitivity of SLND in patients receiving NC. FN rates were improved in patients with US CRs compared to patients with persistent disease on US. No clinicopathologic features were identified that could improve this modality's sensitivity.

Variable	p-value
Chemotherapeutic agent	.82
Primary tumor histology	.95
Presenting clinical T stage	.12
Lymph nodes palpable before therapy	.49
Lymph nodes palpable after therapy	.23
Clinical T stage after therapy	.88

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Hormone Replacement Therapy and Breast Cancer Histology: Does Dose Matter? E.R. Garwood,* A.S. Kumar. *Department of Surgery, Kaiser Permanente - Oakland Medical Center, Oakland, CA.*

Intro: To date, the relationship between dose of hormone replacement therapy (HRT) and breast cancer characteristics has not been examined, although duration of HRT use has been studied extensively. As HRT dosing regimens are not uniform, we hypothesized that a dose-index (summation of tablet dose multiplied by the number of tablets dispensed) may be a more useful marker than duration of use when examining the influence of HRT use on breast cancer. Methods: We conducted a retrospective review on incident cases of female breast malignancy occurring in 2003 registered in a large regional cancer registry (n=2830). HRT type, dose, number of tablets dispensed, tumor receptor status, stage, grade and histology were obtained from electronic records for women >50yrs who had pharmacy data for >1yr (n=1701). Results: Age-adjusted odds ratios for ER+ and PR+ tumors in women with low, medium, and high dose indices for estrogen (E) or progesterone (P) exposure vs. those who were not exposed to HRT found that those with a low dose-index for either E or P exposure had a significant reduction in PR+ tumor occurrence [$p<0.02$ (OR 0.71, 95%CI 0.52-0.95) for E and $p<0.01$ (OR 0.64, 95%CI 0.46-0.88) for P]. This finding echoed the HRT duration analysis that we previously reported in which women exposed to E or P for <6mos had a significant reduction in PR+ tumor occurrence [$p<0.01$ (OR 0.51, 95%CI 0.34-0.77) for E and $p<0.01$ (OR 0.55, 95%CI 0.38-0.79) for P]. In the current analysis there was a trend toward a U-shaped distribution with low index E or P and high index E or P women having the lowest rates of ER+ and PR+ tumors. As in our previous duration-only analysis, we did not find any significant differences in tumor histology among low, medium, and high dose-index exposed women. Conclusion: The cumulative effect of exogenous E and P as calculated by factoring both dose and duration of HRT use prior to breast cancer diagnosis did not reveal associations that were not previously illustrated by our analysis of HRT duration alone. We conclude that the duration of use is an adequate surrogate for determining overall exposure to HRT.

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Post-excision mammography (PEM) is a valuable tool for detecting residual disease M. Morrogh,* A. Park, H.S. Cody III, T.A. King. *MSKCC, New York, NY.*

Introduction Pathological margin assessment is standard practice for assessing the likelihood of residual disease in breast conserving surgery (BCS), however its limitations are well known. In the setting of malignant calcifications, PEM to assess for residual disease has been suggested. The aim of this study was to assess the value of PEM in addition to margin assessment in predicting the presence of residual disease after BCS. Methods From January 2001 to December 2003, 4235 patients underwent breast cancer surgery at MSKCC. Those with suspicious calcifications leading to a diagnosis of breast cancer followed by successful BCS at MSKCC were evaluated for the use of PEM. A total of 328 (8%) patients had PEM and were eligible for review. Margin status was reported by the perpendicular inked technique. Re-excision was undertaken at the surgeon's discretion. Results Of 328 patients, 200 (61%) had DCIS and 128 (39%) had invasive cancer. In total, 119/200 (60%) patients with DCIS underwent re-excision (72/119 (61%) with positive/close margins alone, 31/119 (26%) with close margins + positive PEM, and 16/119 (13%) with negative margins + positive PEM). Residual disease was detected in 55/119 (46%) patients with DCIS. Similarly, 68/128 (53%) patients with invasive cancer underwent re-excision (47/68 (69%) with positive/close margins alone, 14/68 (20%) with close margins + positive PEM, and 9/68 (11%) with negative margins + positive PEM). Residual disease was detected in 30/68 (44%) patients with invasive cancer. In the setting of positive/close margins, positive PEM improved prediction of residual disease at re-excision for patients with DCIS and invasive cancer (Table). In select cases with negative margins, PEM accurately demonstrated occult disease in 6/16 (38%) patients with DCIS and in 3/6 (50%) patients with invasive cancer. Conclusion Given the limitations of pathological margin assessment, PEM is a valuable tool for detecting occult residual disease for patients with in-situ or invasive cancer associated with malignant calcifications. Our data suggests that PEM should be considered in the setting of malignant calcifications, even select in cases with negative margins.

	PPV Margin status alone Positive <2mm ≥2mm	PPV positive PEM alone	PPV Margin status & positive PEM Positive <2mm ≥2mm Negative
DCIS, n=200	74% 41% 26%	54%	70% 57% 33% 38%
Invasive cancer, n=128	52% 35% 67%	54%	67% 45% 67% 50%
Overall, n=328	62% 39% 41%	53%	68% 54% 50% 39%

PPV: positive predictive value for residual disease at re-excision

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Nipple-sparing mastectomy; assessment of 51 procedures T. Tsangaris, A.M. Voltura,* L. Jacobs, C. Balch, G. Rosson, N. Singh, J. Flores, P. Argani. *Johns Hopkins Hopital, Baltimore, MD.*

BACKGROUND: Retrospective studies have shown occult nipple areola complex (NAC) involvement of breast cancer is low, occurring in 8% of women undergoing skin sparing mastectomy (NSM). The cosmetic result and high patient satisfaction of the NSM has prompted further evaluation of the oncologic safety of this procedure. In this study we examined our experience of 51 NSM. METHODS: A retrospective chart review of 36 self-selected patients from 2002 to 2007 who under went NSM was conducted. All patients had NAC margins sent separately for pathologic assessment. We also evaluated tumor size, location, axillary node status, and cosmetic result. RESULTS: Malignant NAC involvement was found in 2 of 34 NSM (5.9%). One involvement was found on frozen section (obtained because of gross suspicion) and the NAC was immediately removed. In the other patient, the NAC involvement was found on permanent section, and the NAC was subsequently excised. 3 patients had locally advanced disease; 1 of whom was found to have distant metastasis and died within the year; another was found to have local reoccurrence at two years. 1 patient was incidentally found to have residual tumor in the lateral incision upon implant exchange six months later. The average tumor size was 2.3 cm for invasive cancer, and 2cm for DCIS. Of the 51 NSM, 17 were for prophylaxis, 11 for DCIS, and 23 for invasive cancer. For invasive cancer, nodes were negative in 15 patients, positive in 7, and unable to be assessed in 1. Overall, 94% of the tumors were located peripherally in the breast. Median follow up was two years. Cosmetic result was noted to be good. CONCLUSIONS: We conclude from these data that NSM is an oncologically safe procedure in specific patients. While patient self-selection may prompt NSM, it should only be performed with strict criteria. Our occurrence of 5.9% NAC involvement correlates with current literature. We continue to develop a formal patient registry, establish specific criteria for selection, and assess current patients for evidence of disease.

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A novel intralymphatic drug delivery system for treatment of locally metastatic breast cancer M.S. Cohen,[1]* S. Cai,[2] Y. Xie,[2] M.L. Forrest.[2] *1. Surgery, University of Kansas Medical Center, Kansas City, KS; 2. The University of Kansas, Lawrence, KS.*

Background: Breast cancer is the second leading cause of cancer death in women. Current chemotherapy agents all carry systemic toxicity either alone or in combination. To date no chemotherapy strategy is targeted to treating intralymphatic spread alone. There is, therefore, a critical need to develop novel drug delivery methods allowing chemotherapeutic agents to remain intralymphatically at therapeutic levels for their duration of action. Methods: Hyaluronan (HA) is a highly biocompatible and nonimmunogenic polymer that follows lymphatic drainage from the interstitial spaces. We formed complexes of HA and cisplatin by a non-covalent conjugate. We determined in vitro release rate of cisplatin from conjugates and cytotoxicity against MDA-MB-231 and MCF7 human breast cancers in cell culture. Complexes were injected subcutaneously into the right upper mammary gland of female Sprague-Dawley rats and the distribution of conjugates determined by atomic absorption spectometry. Results: Conjugates of cisplatin and HA contained up to 26% w/w of cisplatin and released drug with pseudo first order kinetics with a half-life of 10 hours in saline. Cisplatin-HA conjugates had high anti-tumor activity similar to the free drug: HA-cisplatin IC50 7ug/mL (cisplatin basis) in MCF7 and MDA-MB-231 cells (free cisplatin IC50 7 ug/mL). HA-cisplatin conjugates were well tolerated in rodents with no signs of injection site morbidity or major organ toxicity after 24 hours and significantly increased localization compared to cisplatin in saline controls. Conclusions: Cisplatin-HA conjugates demonstrate antiproliferative efficacy similar to standard cisplatin formulation in a breast cancer model in vitro. While toxicity profiles of this nanoparticle delivery conjugate are promising, further evaluation of antitumor efficacy and survival in an in vivo model will be required to validate the benefit of this novel therapy. This contribution is expected to be significant in providing a novel intralymphatic drug delivery method in breast cancer to preferentially treat at-risk regional lymph nodes and avoid systemic toxicities.

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Ongoing clinical use of an intra-operative molecular assay for the detection of metastases in the sentinel lymph nodes of breast cancer patients J.C. Schobbens,* D. Martin Martinez, I. Veys, S. Majjaj, D. Noterman, D. Hertens, V. Filippov, V. Durbecq, J.M. Nogaret, D. Larsimont. *Institut Jules Bordet, Bruxelles, Belgium.*

Intra-operative tests for metastases in sentinel lymph nodes (SLNs) often miss cancer later detected by permanent section H&E, necessitating a second surgery for full axillary lymph node dissection (ALND). A new molecular assay (GeneSearchä BLN Assay, Veridex, LLC) had high sensitivity in U.S. clinical studies, and in a smaller validation study (n= 78) at our institution: assay sensitivity 92.3%, specificity 96.9% compared to H&E. This assay is now commercially available in the EU and is currently being used at our institution for intra-operative ALND decisions. Alternating 2 mm pieces of the SLNs are shared between the assay and H&E. Nodes are transported to the pathology lab via pneumatic tubes and tested by trained assay operators. The tissue for the assay is homogenized, RNA is extracted, and amplification of Mammoglobin and Cytokeratin 19 gene expression is performed and read on a real-time RT-PCR instrument. Post-operatively, in the alternating 2 mm node pieces, 3 sections for H&E are taken at 50 µm intervals. H&E negatives are assessed with immunohistochemistry. Histology and assay results are not expected to have 100% agreement due to testing of different pieces of tissue as well as the limited histological sampling. To date, SLNs from 100 breast cancer patients have been tested intra-operatively. When H&E was positive the assay was positive 84.2% of the time. When H&E was negative the assay was negative 93.8% of the time. Of the resulting ALNDs, 37.5% are positive when histology and the assay agree. When only the assay or histology are positive 0% of ALNDs are positive. The assay result averages 39 minutes from the time the node is removed from the patient. These results indicate that this new molecular test has consistently high performance and can be effectively employed in the clinical setting to avoid second surgery ALNDs for patients (about 16%) who would normally have nodal metastases detected later with H&E. This will spare the patient additional days in the hospital. Also, the node evaluation is more thorough than is practical by histology alone, potentially benefiting treatment decisions.

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The Role of Ultrasound Guided Fine Needle Aspiration of Axillary Nodes in the Staging of Breast Cancer A. Jain,[1]* T.N. Tsangaris,[2] N. Khouri,[2] L.K. Jacobs.[2] *1. Surgery, University of Maryland, Baltimore, MD; 2. Johns Hopkins University, Baltimore, MD.*

Introduction: Ultrasound guided fine needle aspiration (USFNA) has been used to evaluate suspicious appearing lymph nodes in lieu of sentinel node biopsy. We evaluated whether USFNA could reliably predict the pathologic status of suspicious or normal appearing axillary lymph nodes. We hypothesized USFNA would be accurate for breast tumors larger than 2 cm. Methods: We retrospectively reviewed 68 patients with 69 preop USFNAs from 2003 to 2005. The results of 65 preop USFNAs were compared with the results of SNLD or axillary node dissection (ALND) for concordance. Four USFNAs were excluded because of a complete response to neoadjuvant therapy. We evaluated if primary tumor features (histology, size, grade, vascular invasion, estrogen/ progesterone receptor status and Her-2-neu status) predicted concordance of USFNA and the final lymph node pathology. Results: Of 65 axillae analyzed, 39 (60%) were positive, 4 (6%) were nondiagnostic, and 22 (34%) were negative by USFNA. Overall, USFNA had 78% sensitivity, 100% specificity, and 100% positive predictive value (PPV). In patients with palpable or ultrasonographically suspicious nodes, USFNA had 89% sensitivity, 100% specificity, and 100% positive predictive value (PPV). When the subset of patients with nonpalpable or radiologically nonsuspicious nodes was analyzed, USFNA sensitivity dropped significantly to 54% while specificity and PPV remained 100%. USFNA of clinically or radiologically nonsuspicious nodes has similar sensitivity, specificity, and PPV as clinical exam in our series (Clinical exam: sensitivity 50%, specificity 96%, and PPV 96%). Tumor grade (not size) predicted concordance of USFNA and SLND/ALND results (p=0.046). Conclusions: USFNA of axillary nodes has high specificity and PPV in clinically or radiologically suspicious nodes. Sensitivity of USFNA is low (50%) for normal appearing nodes, but positive USFNA may allow definitive management of the axilla without a SLND. Subset analysis of our data suggests that the relatively high overall sensitivity of "random" USFNA reported in our series (78%) and some other series may be the result of selection bias (sampling of suspicious nodes).

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Office Ductoscopy for surgical selection in women with Pathologic Nipple Discharge A. Mangat,* A. Rivers, B. Susnik, S.A. Khan. *Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL.*

INTRODUCTION: The standard approach to women with pathologic nipple discharge(PND)is surgical duct excision for definitive diagnosis. Imaging studies are of limited value. We conducted a prospective study to evaluate the role of office ductoscopy to select patients for surgery. METHODS: Women with PND were defined as meeting at least 2 of 3 criteria: single duct, spontaneous, serous/bloody discharge. If a significant lesion was seen on office ductoscopy, they were offered surgical resection. If no significant lesion was present, they were offered observation. RESULTS: 64 women with PND (mean age 48 years) underwent ductoscopy. Of these, 37/64 (58%) underwent surgery, and 27/64 (42%) were observed. In the surgical group, 27/37 (73 %) had no relevant findings on imaging, but significant findings on ductoscopy was strongly related to the recommendation for surgery(p=0.001). In the surgical group, 6 women (17%) had an invasive or non-invasive ductal carcinoma, in 4 of whom there were no relevant findings on pre-operative imaging. One or more intraductal papilloma was found in 25/37 (68%), 2/37 had florid ductal hyperplasia (5%) and 4/37 (11%) had non-proliferative findings on pathology although a papilloma was seen on ductoscopy. Thus proliferative/neoplastic disease was found in 89% of women. In the observation group, mean follow up of 14.3 months is available on 26 of the 27 patients, and 21 of these (78%) are doing well with no further nipple discharge or other breast complaints, 4/27(15 %) now have non-pathologic nipple discharge, 1/27 (3.5 %) had surgical intervention elsewhere (no malignancy found) and one patient was lost to follow up. CONCLUSIONS: Our data reveal a substantial yield of malignancy (17%) with ductoscopy-guided surgical resection, and suggest that close observation may be offered to patients with PND who have no significant lesions on ductoscopy or imaging. These findings require verification in a larger study with longer follow-up.

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Comparative analysis of time delays to initiation of chemotherapy in women undergoing oocyte retrieval with cryopreservation J.L. De la Pena,* A. Madrigrano, L. Westphal, I.L. Wapnir. *of Surgery, Stanford University, Stanford, CA.*

Introduction: As outcomes in breast cancer survival improve so have expectations for protecting future childbearing from the effects of adjuvant therapies. The necessity to delay pregnancy for years after diagnosis and treatment, and the fear of losing fertility are important factors motivating women to seek cryopreservation of fertilized eggs or oocytes. The impact of fertility consultation and oocyte retrieval (FCOR) on the timing of surgery and adjuvant chemotherapy was examined in this group of women and compared to women who did not receive FCOR (non-FCOR). Methods: We retrospectively identified women <40 years of age who were diagnosed with breast cancer and received adjuvant chemotherapy postoperatively. The time intervals between first diagnosis, timing of surgery, fertility consultations/interventions and initiation of adjuvant chemotherapy were noted. Unpaired T-test was used for group comparisons of mean time intervals. Results: A total of 44 women were identified, 29 who did not undergo FCOR, and 15 who underwent FCOR in the same time period. 13.3% of FCOR group already had children compared to 17/29 (58.6%) in the non-FCOR group. The average time from initial diagnosis to fertility consultation was 27.7 days (0-133) and from referral to egg retrieval 31.1 days (13-57). The mean time interval from definitive surgery to chemotherapy in FCOR vs. the non-FCOR group was 35.9 and 29.2 days (p<0.2257). In the 26 to 30 age group, the time interval from surgery to chemotherapy was 36 (FCOR) and 35.5 (non-FCOR) days, for women ages 31 to 35, 43 and 24.3 and for the 36 to 39 age group 35.9 and 29.2 days, respectively. There were no statistically significant differences in these subset analyses. Five of the 15 women underwent FCOR prior to definitive surgery. Their time interval from diagnosis to definitive surgery was 55.8 days compared to 51.9 days for the non-FCOR patients. Conclusions: The time investment required for women to undergo ovarian stimulation/egg retrieval and cryopreservation does not appear to measurably delay time to adjuvant chemotherapy when compared to same age women who did not undergo this procedure.

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The Prognostic Value of Lymph Node Yield in Well-Differentiated Thyroid Carcinoma S.R. Martinez,* S.L. Chen. *UC Davis Cancer Center, Sacramento, CA.*

Introduction: The role of routine lymphadenectomy is controversial in well-differentiated thyroid carcinoma (WDTC). The prognostic importance of the number of lymph nodes harvested at surgery (lymph node yield) is unknown. We hypothesized that overall survival in WDTC is influenced by the lymph node yield at thyroidectomy. Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify all patients who underwent total or near-total thyroidectomy with at least one lymph node examined for WDTC between 1988 and 2004. Kaplan-Meier survival curves for lymph node yield (1-9 vs ≥ 10) stratified by nodal status were compared using the Log Rank test. A multivariate classification and regression tree (CART) analysis including patient age, gender, extent of disease (limited to thyroid vs. extracapsular extension), tumor size, radiation treatment, nodal status, and lymph node yield was performed to determine the lymph node yield that was most prognostically important. Results: The database was used to identify 12,418 WDTC patients who underwent thyroidectomy and lymphadenectomy. Of these, 6,736 patients (54%) had lymph node metastases. The median number of lymph nodes evaluated was 3. Lymph node yield was significantly associated with improved overall survival in node-negative (Log Rank, $P < 0.001$) and node-positive patients (Log rank, $P < 0.02$). On CART analysis, increasing lymph node yield remained a statistically significant predictor of overall survival ($P < 0.001$) in node-negative patients only. A lymph node yield of ≥ 4 but ≤ 61 was particularly associated with improved survival (Hazard Ratio = 0.78) in these patients. Conclusions: The number of lymph nodes harvested and examined at thyroidectomy is significantly associated with WDTC survival. The number of lymph nodes harvested and examined at thyroidectomy is significantly associated with WDTC survival. For node negative patients, sampling at least 4 nodes may improve staging accuracy.

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In vitro chemoresistance testing in well-differentiated carcinoid tumors J.M. Lyons,[1]* J. Abergel,[2] J.L. Thomson,[3] Y. Wang,[1] L.B. Anthony,[1] J.P. Boudreaux,[1] R. Warner,[2] E.A. Woltering.[1] *1. Louisiana State University Health Sciences Center, New Orleans, LA; 2. Mount Sinai School of Medicine, New York, NY; 3. USDA ARS Southern Regional Research Center, Baton Rouge, LA.*

INTRODUCTION: Well differentiated (typical) carcinoid tumors have a very poor response to chemotherapy in clinical trials. We hypothesized that tumor specimens from well differentiated carcinoid tumors would be highly resistant to the effects of chemotherapy when tested against a variety of antineoplastic agents in vitro. METHODS: 98 typical carcinoid specimens were surgically harvested, cultured, and tested against antineoplastics in vitro. 3H-Thymidine incorporation was used to assess the percentage of cell-growth inhibition (PCI) of tested specimens. PCI was used to determine if specimens had extreme drug resistance (EDR), intermediate drug resistance (IDR), or low drug resistance (LDR) to each reagent against which they were tested. RESULTS: 70 specimens generated results. Each was tested with an average of 6 drugs. The mean proportions of drugs classified as LDR, IDR, and EDR were 0.48 (range 0 to 1), 0.34 (range 0 to 1), and 0.18 (range 0 to 0.80), respectively. The mean numbers of drugs per specimen classified as LDR, IDR, and EDR chemoresistance were 2.7, 2.1, and 1.2, respectively. 57 (81%) of 70 of specimens had LDR to at least 2 drugs. 5-FU had the highest frequency of low chemoresistance at 69%, followed by Doxorubicin at 67%. CONCLUSION: Low in vitro resistance to antineoplastics was prevalent among typical carcinoids while EDR was comparatively infrequent. This implies that there may be less clinical chemoresistance and more chemosensitivity among typical carcinoid tumors than clinical trials have previously revealed. These findings warrant additional investigations assessing the clinical response of patients with carcinoid to assay-guided chemotherapy regimens.

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Outcomes of Central Neck Dissection in Thyroid Cancer E.A. Fialkowski,* J.F. Moley. *General Surgery, Washington University School of Medicine, Saint Louis, MO.*

Introduction: The role of routine central lymph node (level VI) dissection (CND) in operations performed for thyroid cancer has recently been strongly

debated among endocrine surgeons. Methods: This study is an IRB approved review of a prospectively maintained thyroid cancer database and patient medical records. Results: A total of 241 CNDs for thyroid and parathyroid cancer were performed between 1992 and 2006. This includes 87 dissections performed with initial thyroidectomy, and 154 re-operations (174 medullary, 59 papillary, 4 parathyroid cancer, 4 other). Recurrent laryngeal nerve (RLN) injury occurred in 1.1% of initial operations, and in 2.6% of re-operations. Permanent hypoparathyroidism occurred in 0% of initial operations and in 5.6% of re-operations. Complications that occurred only in patients with pre-existing vocal cord palsy included laryngospasm requiring reintubation (4 patients), tracheal laceration and innominate artery blow-out (one patient). There were no deaths. Long-term follow-up was available for 163 patients (average follow-up 4.6 years). Central recurrence of cancer occurred in two patients after initial CND, and in 12 patients following re-operation. Recurrence was not observed when the initial dissection contained negative nodes. When central nodes were positive, however, central recurrence occurred in 12.4%, and lateral neck recurrence occurred in 26.5%. Conclusions: Complications of CND are more common in re-operations, and in patients with pre-existing vocal cord palsy. Positive central nodes are associated with a significant risk of recurrence in the central and lateral neck. The data suggests that CND performed with initial thyroidectomy may reduce the risk of central and lateral recurrence.

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Optimizing strategy for successfull parathyroidectomy: pre-operative scintigraphy combined with additional ultrasound/CT of the neck if necessary B. Twigt,* T. VDalen. *Diakonessenhuis, Utrecht, Netherlands.*

Minimally invasive parathyroidectomy (MIP) is the preferred operation for patients with primary hyperparathyroidism and positive preoperative imaging. Imaging may consist of scintigraphy, ultrasound and CT. Although the goal is a successful operation, proven by postoperative eucalcemia and decline of symptoms, we state that this should be reached by a careful strategy, giving as much information to perform a successful operation, but doing this against reasonable costs and as little negative side-effects. We investigated the following strategy. Scintigraphy. followed by ultrasound and/or CT scan of the neck if necessary. We didn't use a gamma probe or intraoperative PTH measurements. Prospective data collection took place of 62 consecutive patients operated between 2001 and 2007. Scintigraphy showed unilateral uptake in 46 patients. In 14 cases no adenoma was found and in 2 there was doubt about localization. Additional ultrasound and/or CT revealed 7 more adenoma's. There was equivalence of imaging in 84%. MIP was performed in 57 patients and conventional neck exploration (CNE) in 5 patients. 12 patients needed conversion. In 58 patients (93%)one adenoma was found and in 2 patients had multiglanddisease (MGD) (3%). In one patient there was a parathyroid carcinoma and in one the adenoma wasn't found. In 3 patients (5%) there was persistent hypercalcaemia. In one of them because of MGD, in two because the adenoma wasn't found. Two of them underwent conventional exploration and became normocalciemic. The third refused further operation. Sensitivity raised from 75% to 88% when scintigraphy was followed by additional imaging. The overall succesrate is 98%. Scintigraphy and the combination of ultrasound and a CT scan are complementary. If scintigraphy does not show an adenoma, additional combination of ultrasound and/or a CT improves sensitivity from 75% to 88%. With this allgoritm we succesfully treated 62 consecutive patients, with an overall succesrate of 98%. Proving that in spite of a negative scintigraphy, MIP is possible and succesful in most patients.

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Carcinoid Tumors of the Appendix: A Population-Based Study J.T. Mullen.* *Surgery, Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Carcinoid tumors of the appendix are rare, and as such there are few data guiding the current recommendations for the optimal extent of their surgical treatment. Methods: All patients with malignant, typical carcinoid tumors of the appendix for whom complete data were available in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2003 were analyzed. Clinicopathologic factors predicting lymph node (LN) involvement and survival were determined. Results: Eighty-nine of 179 patients reported to the SEER program had complete clinicopathologic data and follow-up. The majority of patients were female (73%), < 50 years of age (69%), and Caucasian (87%). LN metastases were present in 44 (49%) of 89 patients, including 4 (15%) of 27 patients with tumors ≤ 1 cm, 16 (47%) of 34 patients with tumors > 1 cm but ≤ 2 cm, and 24 (86%) of 28 patients with tumors > 2 cm. Increasing tumor size ($p < 0.0001$) predicted LN involvement, whereas age, gender, and depth of tumor invasion did not. Most patients had localized (37%) or regional (54%) disease; only 9% of patients had distant metastases (DM). Male gender ($p = 0.004$) and age ≥ 50 years ($p = 0.001$) were associated with an increased risk of DM. Excluding patients with DM, the 10-year disease-specific survival (DSS) of patients with negative LNs and tumors of any size was 100%, and the 10-year DSS of patients with positive LNs and tumors ≤ 1 cm, > 1 cm but ≤ 2 cm, and > 2 cm was 100%, 92%, and 91%, respectively. The 5-year DSS of patients with positive LNs and no DM who underwent right hemicolectomy (RHC) ($n = 28$) was 100% versus 76% ($p = 0.006$) for those who underwent less than a RHC ($n = 8$). Conclusions: Regional LN metastases in patients with appendiceal carcinoids ≤ 2 cm in size is much more common than previously recognized, but their impact on survival is uncertain. While appendectomy alone is certainly adequate treatment for appendiceal carcinoids ≤ 1 cm in size, RHC should be performed in patients with tumors > 1 cm in size given their high incidence of LN metastases and the apparent survival benefit this procedure confers.

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Differential Gene Expression in Sestamibi Positive vs. Negative Parathyroid Adenomas B.R. Untch,* M.E. Barfield, C.L. Tebbit, J.A. Olson. *Surgery, Duke University Medical Center, Durham, NC.*

Introduction: Technetium 99-m sestamibi scanning allows preoperative localization of parathyroid adenomas in 75-90% of cases of primary hyperparathyroidism. Several studies have identified patient and tumor characteristics that correlate with sestamibi uptake; however, molecular determinants of sestamibi uptake in parathyroid adenomas are unknown. In a gene discovery approach, we used microarray technology to examine differential gene expression in sestamibi positive (SP) versus negative (SN) parathyroid adenomas. Methods: Global gene expression in 20 SP and 23 SN parathyroid adenomas were assessed by hybridization to spotted oligonucleotide microarrays (Operon V1 or V3 arrays). Binary regression was used to generate a gene expression signature and generate validation probabilities (Matlab R2006a, Natick, Massachusetts). Gene expression signature analysis was also performed (Ingenuity Systems Inc., Redwood City, CA). Clinicopathologic data was reviewed retrospectively. Results: Binary regression analysis of the Operon V1.0 samples ($n=26$; 12 SP and 14 SN) identified a 50 gene signature that predicted sestamibi positivity in cross-validation studies (sensitivity 92% and specificity 79%). Validation of the signature on an independent sample set (Operon V3.0 platform, $n=17$; 8 SP and 9 SN) demonstrated similar results (sensitivity 88% and specificity 67%). In silico gene signature analysis identified cell to cell signaling ($p<0.001$) and cellular organization ($p<0.001$) as signature descriptors. Subsequent in silico molecular pathway analysis of these genes revealed TNF, growth hormone and Wnt/β-catenin pathway interactors. Age, sex, race and routine preoperative laboratory values were not different between the SP and SN groups. However, gland weight was greater in the SP group ($p=0.04$) as was the incidence of glands in the lower position ($p=0.02$). Conclusions: This study confirms data showing a correlation between gland size and SP. Sestamibi uptake in primary hyperparathyroidism maybe influenced by tumor size, tumor location and differential gene expression. Pharmacologic manipulation of molecular pathways may be a strategy to improve sestamibi uptake in parathyroids.

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Molecular markers that predict progression free survival in elderly women treated with primary hormone therapy for oestrogen receptor positive breast cancer V. Garimella,[1]* S. Radhakrishna,[2] P.L. McManus,[2] J.N. Fox,[2] T.K. Mahapatra,[2] P.J. Drew,[1] L. Cawkwell.[1] *1. Cancer Biology Proteomics Group, University of Hull, Hull, United Kingdom; 2. Hull and east Yorkshire Hospitals NHS Trust, Hull, East Yorkshire, United Kingdom.*

Background: Women over the age of 80 years have the highest risk of breast cancer (1 in 10). However, large randomised trials of breast cancer treatment both in the USA and Europe have very few patients recruited from this age group. Principles of breast cancer treatment in women over 80 years are extrapolated from the data from younger women. Breast cancer in the elderly has distinct features like presentation at a later stage, tumours being ER and PR pos-

itive, biologically less aggressive and lymph node metastases less frequent and not as important factor in determining survival. Patients and Methods: A total of 47 elderly women with a diagnosis of ER positive breast cancer who were treated with primary hormone therapy (Letrozole) as sole therapy were identified from a prospectively maintained registered cancer database. Two patients had bilateral breast cancer. Archival formalin fixed paraffin embedded tumour tissue from diagnostic core biopsies was obtained for these 49 cases of breast cancer. Immunohistochemical analysis using avidin-biotin complex method for PR, p53, Her2, EGFR and Bcl2 was performed. Results: The mean age of the patients was 81.5 years (62.8-93.9) and mean duration of follow up was 31.5 months (8.2-53.3). Complete clinical response was seen in 33% (16/49), partial response in 24.5% (12/49), stable disease was seen in 24.5% (12/49) and progressive disease in 19% (9/49). Of the 49 breast cancers treated, progression free survival was seen in 82% (40/49) of the cases. Univariate analysis of expression of the molecular markers with progression free survival was performed using Fisher's exact test. This showed that PR positivity (p=0.016) and p53 negativity (p=0.037) significantly correlated with progression free survival. Multivariate stepwise logistic regression analysis also showed p53 and PR to significantly predict progression free survival. This pilot study showed that PR and p53 expression can be used to predict response to primary aromatase inhibitor therapy in elderly women with ER positive breast cancer.

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Bilateral Adrenalectomy: A Successful Long-Term Treatment Option for Ectopic ACTH Syndrome R.S. Sippel,[1]* D.M. Elaraj,[2] S. Lindsay,[2] E. Kebebew,[2] J. Tyrrell,[2] Q.Y. Duh.[2] *1. Surgery, University of Wisconsin, Madison, WI; 2. University of California- San Francisco, San Francisco, CA.*

BACKGROUND: Patients with ectopic ACTH (eACTH) syndrome suffer from debilitating symptoms due to cortisol excess. When the primary source of the ACTH secretion is not found or cannot be resected, bilateral adrenalectomy is a treatment option. This study looks at the long-term benefits of this treatment option. METHODS: Between 02/1995 and 05/2007, 10 patients underwent a laparoscopic bilateral adrenalectomy for treatment of eACTH syndrome. Preoperative and operative variables were collected from a prospective database. Long-term follow-up was obtained via patient survey. RESULTS: The mean age of the patients was 46 (70% female). The mean time from diagnosis to surgery was 17.7 mos (1-72 mos). At the time of their operation, 5 patients had an unknown source, 4 patients had unresectable metastatic disease (3 neuroendocrine, 1 breast), and 1 patient was too sick to undergo a thoracotomy. The mean pre-operative ACTH level was 225 mcg/dL and 24-hr urinary cortisol was 6890 mcg. Surgery was successful in all patients, with a mean length of stay of 4.9 days. Three patients had post-operative complications (2 pneumonia, 1 Addisonian crisis), there were no long-term complications. Follow-up was obtained on all patients with a mean follow-up of 54 mos (9-135). Six of ten patients are alive (3 patients never had their tumor found, 2 are living with metastatic disease, and 1 went on to resection of his tumor). The 4 patients that died (3 died of disease) lived an average of 42 mos (18-56 mos) after surgery. Symptomatic improvement was dramatic in all patients: 7/7 with diabetes were cured, 6/9 patients with HTN were cured (3/9 improved), 7/10 with weakness resolved, and 7/8 with depression were cured. Physical signs including buffalo hump, facial plethora, moon facies, hirsuitism, and acne resolved in all patients. Five of the six patients that are still alive stated that the surgery had dramatically improved their quality of life. CONCLUSIONS: Bilateral adrenalectomy is often considered a last resort in patients with eACTH production. However laparoscopic bilateral adrenalectomy can be done safely and can provide excellent long-term palliation for patients.

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A Review of 142 Cases Of Thyroid Cancer In An Ethnically Diverse Population Over A 16 Year Period D. Brief,* C. Boutros, M. Myatt. *Surgery, NewarkBeth Israel Med.Ctr., Newark N.J., NJ.*

.A review of our experience with thyroid cancer in an inner city hospital revealed an ethnically diverse population grou consisting of 46 Afro-Americans, 73 Caucasians, and l3 Hispanics.10 patients race were unclassified. A review was undertaken to see if race played any role in treatment paradigms or outcomes. Our results showed over the l6 year period from l989-2005 showed papillary cancer in l04 patients(73%),follicular cancer in 19 patients(13%) 4 with oxyphilic adenocarcinoma, 3 with primary non-hodgkins lymphoma, 3 with sporadic non-familial medullary carcinoma, and 4 with anaplastic large cell lymphoma. The majority of cases in the differentiated cancers were Stage I and II (63% in the papillary group and 67% in the follicular cases) The mean followup was 65.1 months. l2(ll%) of the papillary goup and 3 (15%) of the follicular group. All of the anaplastic carcinomas died.,Several surgeons and numerous senior residents wereinvolved in tne operative treatment. There were no operative deaths.Surgicaltreatment wassub total thyroidectomy in 55% of cases and total thyroidectomy in 45% of cases. 37 patients received radioactive iodine after surgeryin the total thyroidectomy group and 7 patients received radioactive iodine in cases where less than total thyroidectomy group. There were no operative deaths. There were 3 recurrent laryngeal nerve injuries in the total thyroidectomy group, 2 were transient.. There were no recurrent laryngeal nerve injuries in thesubtotally resected group. ll patients all in the total thyroidectomy grooup had post operative hypocalcemia,5 of them were transient. No cases in the subtotal group were hypocalcemic. There were no statistical differences between racial groups in their stage at presentation, Treatment paardigms used and outcomes in this group of patients. In conclusion race did not play any significant role in the managment or outcomes in this group of patients. Excellent surgical results were achieved w'ith a variety of surgical procedures, but Total thyroidectomy with post operative radiation is our preferred treatment except for small or biologically insignicant microscopic differentiated cancers.

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Intraoperative Blood Loss Predicts Survival Independently of Allogeneic Transfusion Following Resection of Hepatocellular Carcinoma S.C. Katz,* K.H. Liau, M. Gonen, J. Shia, W.R. Jarnagin, Y. Fong, M.D. D'Angelica, L.H. Blumgart, R.P. DeMatteo. *Surgery, Memorial Sloan-Kettering, New York, NY.*

INTRODUCTION: While several studies have addressed the impact of blood transfusion on oncologic outcome following liver resection for hepatocellular carcinoma (HCC), the independent effect of intraoperative estimated blood loss (EBL) is unknown. We therefore assessed the correlation between the amount of blood loss during HCC resection and survival. METHODS: From our prospective database, we identified 193 patients who had a partial hepatectomy for HCC from 1985-2003. Clinicopathologic factors were analyzed as predictors of EBL and outcome using logistic regression. Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were assessed using the Kaplan-Meier method. RESULTS: The median patient age was 64 (range 19-86) and 66% were male. All patients had histologically proven HCC, with all but 5% being Child-Pugh class A. The median follow-up times was 34 months (range 1-297). Factors associated with increased intraoperative EBL on multivariate analysis were liver necrosis/inflammation, extent of hepatectomy, operative time, and vascular invasion ($p<0.05$). Tumor size, vascular invasion, and intraoperative EBL were significant predictors of OS and DSS on univariate analysis ($p<0.05$). DFS was significantly decreased in patients with >1 liter EBL ($p<0.05$). EBL >1 liter remained a significant predictor of OS and DSS following exclusion of patients who underwent transfusion or those with vascular invasion ($p<0.05$). On multivariate analysis, EBL>1 L, tumor size>5cm, and vascular invasion were each independent predictors of decreased DSS (Table). Additionally, we found a significant inverse correlation between increasing levels of EBL and length of DSS ($p<0.05$). CONCLUSIONS: The amount of blood loss during HCC resection is related to characteristics of both the tumor and the liver parenchyma. Increased intraoperative blood loss during HCC resection is significantly associated with decreased DSS and OS independently of allogeneic transfusion, vascular invasion, or tumor size.

		Median DSS (months)	Univariate	Multivariate
Vascular Invasion	Absent	117	<0.001	0.01
	Present	33		
Allogeneic Transfusion	No	55	NS	-
	Yes	40		
Tumor Size	≤5 cm	100	0.02	0.05
	>5 cm	39		
Blood Loss	≤ 1 L	72	<0.001	0.04
	> 1 L	25		

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Surgical Management of Hepatocellular Adenoma : A Single Institutional Experience S.W. Cho,* J.W. Marsh, S. Holloway, J. Heckman, D.A. Geller, T.C. Gamblin. *Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Hepatocellular adenoma (HA) is a rare benign tumor of the liver, and surgical resection is indicated to reduce risks of hemorrhage and malignant transformation. We sought to evaluate clinical presentation, surgical management and outcomes in patients with HA. Methods: We performed a retrospective review of patients with HA diagnosed on final pathology. Results: 42 patients (39 females) underwent surgical resection for HA between 1988 and 2007. Median age at presentation was 36 years (19-65). Presentations include abdominal pain (29), incidental radiological finding (8), abnormal liver function test (3), and incidental laparoscopic finding (2). 12 patients had hemorrhage from HA, eight of whom underwent emergent hepatic resection. 23 patients reported oral contraceptive use, 1 patient had glycogen storage disease and 2 patients had Turner syndrome. Median number of HA seen on CT scan was 1 (1-10). Median size of HA was 9 cm in diameter (1-18). Operative procedures performed included 9 cases of laparoscopic hepatic resection (lobectomy (1), bisegmentectomy (5), segmentectomy (1), wedge resection (2)), and 33 open cases (liver transplantation (1), trisegmenectomy (3), lobectomy (15), bisegmentectomy (7), segmentectomy (4) and wedge resection (3)). Median estimated blood loss was 300 cc (50-3400). Median length of stay for open cases was 6 days (3-15) and for laparoscopic cases was 3 days (1-7). Morbidity included pleural effusion requiring percutaneous drainage (n=2), pneumonia (n=1), wound infection (n=1) in the open cases, and no morbidity noted in the laparoscopic cases. There was no perioperative mortality. Two patients had hepatocellular carcinoma arising from HA. Six patients had coexistent HA and focal nodular hyperplasia in the resected specimen. Median follow-up was 24 months (1-194), and all patients were alive. Conclusions: This is one of the largest single institution reports of patients with HA who were surgically managed and shows that HA hemorrhage occurs frequently. This report provides evidence that a laparoscopic approach can be utilized in selected cases with low morbidity and short length of stay.

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Neo-adjuvant chemotherapy and surgery for esophageal adenocarcinoma: prognostic value of circumferential resection margin (CRM) and stratification of N1 category A.K. Saha,[1]* C. Sutton,[1] O. Rotimi,[2] H.M. Sue-Ling,[1] S.P. Dexter,[1] A.I. Sarela.[1] *1. Department of Surgery, The General Infirmary at Leeds, Leeds, West Yorkshire, United Kingdom; 2. Department of Histopathology, The General Infirmary at Leeds, Leeds, West Yorkshire, United Kingdom.*

INTRODUCTION In the UK, it is standard practice to treat esophageal adenocarcinoma with neo-adjuvant chemotherapy (no radiation) followed by surgery. We examined the prognostic value of CRM involvement and stratification of the N1 category into 1-4 or ≥5 nodes. METHODS From January 2000-December 2006, 105 patients with radiologically-staged T3, T4 or N1 adenocarcinoma of the gastroesophageal junction (Siewert types 1 or 2) had pre-operative treatment with 5FU and cisplatin.101 patients had an Ivor Lewis operation with 2-field lymphadenectomy, 3 had a trans-hiatal operation and 1 had a 3-incision operation. CRM was assessed by painting the outside of the specimen with India ink and transverse sections at 5-10 mm intervals. The CRM was positive (CRM+) if malignant cells were within 1mm of the inked margin. RESULTS There were 87 men. Median age was 61 years (37-81). Three patients had complete pathological response (T0). Median lymph node yield was 28 (4-77) and 86 patients (83%) had ≥18 nodes. Seventy-four patients (70%) had N1 disease with 1-4 involved nodes in 41 patients and ≥5 nodes in 33 patients. Thirty-eight patients (31%) were CRM+. There was no R2 resection and 1 in-hospital death. Estimated survival at 3 years was 52%, with median survival of 41 months. Alive patients had median follow-up of 30 months (6-76). On Cox univariate analysis, T category (T0/T1/T2 vs. T3/T4; HR 3.1, 95% CI 1.4–6.7), N category (N0 vs. N1; 3.7, 1.5–8.8) and CRM status (CRM– vs. CRM +; 3.6, 1.9–6.6) were significant factors. On multivariate analysis, N category (N0 vs. N1; HR 4.3; 3 year survival 78% vs. 40%, P=0.002) and CRM status (CRM- vs. CRM +; 2.8; 65% vs. 25%, P=0.004) retained independent significance. N1 (1-4 nodes) had significantly longer survival than N1 (≥5 nodes) (52% vs. 32%, P=0.007). For N1 (1-4 nodes), CRM- had significantly longer survival than CRM+ (69% vs.17%, P=0.001). For N1 (≥5 nodes), CRM- had 3 year survival of 38% as compared with 13% for CRM+ (P=0.06). CONCLUSIONS CRM involvement and stratification of N1 category into 1-4 nodes or ≥5 nodes are important prognostic factors.

Pathological characteristics

	pCR/ pT0	pT1	pT2	pT3/pT4	Totals
N0 CRM +	0	0	1	4	5
N0 CRM -	2	6	8	9	25
1-4 nodes CRM +	0	0	0	16	16
1-4 nodes CRM -	0	6	6	13	25
≥ 5 nodes CRM +	0	0	1	16	17
≥ 5 nodes CRM -	1	1	3	12	17
TOTALS	3	13	19	70	105

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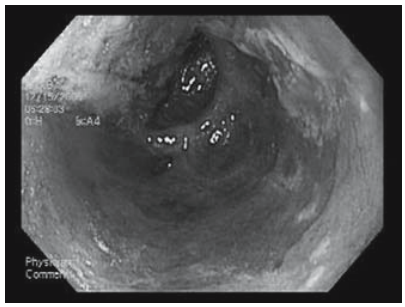
CARCINOMA AND BARRETT'S ESOPHAGUS IN THE ESOPHAGEAL STUMP AFTER GASTRIC PULL-UP IN ACHALASIA PATIENTS: A STUDY BASED ON 10 YEARS FOLLOW-UP J.R. Da Rocha,* U. Ribeiro Jr, S. Szachnowicz, R.A. Sallum, V.N. Felix, I. Cecconello. *Gastroenterology, University of São Paulo Medical School, São Paulo, São Paulo, Brazil.*

Introduction: Esophageal cancer prevalence is high in patients with achalasia. Esophageal resection with gastric pull-up is the principal treatment for advanced stages. The mucosal alterations in the esophageal stump are not completely understood. Aim: To analyze the mucosal alterations in the esophageal stump over chagasic achalasia after esophagectomy with gastric pull-up. Methods: A hundred patients with advanced chagasic achalasia submitted to esophagectomy and cervical gastroplasty were followed up prospectively in a period ranging from two to forty years (mean – 10.6 years). All patients underwent clinical and endoscopic evaluation concerning duodenogastroesophageal reflux and histopathologic aspects of the cervical esophageal stump. Results: Esophagitis in esophageal stump was: 53.6% at the first year; 41.6 % from one to five yrs; and 23.0% from five to ten yrs and 20.9% at more than ten yrs. Gastritis occurred in 21.2% at the first year, 30.0% at five yrs and 35.3 % at ten or more yrs. The occurrence of Barrett's esophagus in the esophageal stump rose over time: none at first yr, 11.1% from two to five yrs and 28.3% from five to ten yrs and 54.7% at more than ten yrs. There were an association between Barrett's esophagus and presence of esophagitis, high gastric acid secretion and gastrin levels ($p<0.001$). Among the patients with chronic esophagitis, three have had developed squamous cell carcinoma in the esophageal stump. Two cases had developed intra-mucosal adenocarcinoma over Barrett esophagus in the esophageal stump and were treated successfully by endoscopic resection. Conclusions: 1.The incidence of Barrett's Esophagus, rose over time. 2. Late complications due to duodenogastroesophageal reflux and higher prevalence of cancer in achalasia, demands long-term endoscopic follow-up. 3. Esophagectomy with gastric pull-up provides good laborative and nutritional conditions in all patients and dysphagia resolution at very long term follow-up (>10 yrs). 4. Endoscopic follow-up with biopsies permitted early diagnosis of the malignancies.



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Response to Neoadjuvant Chemotherapy Predicts Survival Following Resection of Hepatic Colo-Rectal Metastases Better than the Traditional Clinical Risk Factors M. Ben-Haim,[1]* R. Small,[1] N. Lubezky,[1] E. Shmueli,[1] A. Figer,[1] D. Aderka,[2] R. Nakache,[1] J.M. Klausner.[1] *1. Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel; 2. Sheba Medical Center, Tel-Hashomer, Israel.*

Objective: To determine predictors of outcome in patients with metastatic colorectal cancer (CRC) treated by neoadjuvant chemotherapy and surgery. Background: The prognosis of patients following resection of CRC metastases to the liver has traditionally been predicted by clinical risk factors, such as the Memorial Sloan-Kettering Cancer Center Clinical Score (MSKCC-CS, including: number of metastases, size of largest metastases, lymph node status, CEA level and disease-free interval). However, in the era of contemporary neoadjuvant chemotherapy, the clinical scoring system needs re-validation and the role of treatment related factors as prognostic indicators should also be investigated. Methods: Retrospective study including patients with CRC liver metastases, who received oxaliplatin or irinocetan based neoadjuvant chemotherapy and underwent R0 resection of liver metastases. Patients were followed by CT and PET-CT, before, during and after chemotherapy and surgery. The predictive value of the MSKCC-CS and of the degree of response to chemotherapy (measured by CT and PET-CT), were analyzed by univariate and multivariate COX regression. Results: Included are 54 patients, average age, 60 (range 24-80), mean MSKCC clinical score, 1.5 (range 1-5). Overall 1, 2, 3-year survival rates 88%, 70%, and 39%, respectively. Response to chemotherapy on CT was found to be a significant predictor of overall survival on both univariate (p=0.03) and multivariate analysis (p=0.03), whereas the MSKCC-CS and response to chemotherapy on PET-CT were not. Multivariate analysis also demonstrated response to chemotherapy as a predictor of time to recurrence on CT (p=0.02) & PET-CT (p=0.03), while the MSKCC-CS (p=0.64) was not. Conclusions: In this cohort of patients treated with neoadjuvant chemotherapy, the outcome was not predicted by the traditional clinical scoring system, but rather by response to chemotherapy as evaluated by CT and PET-CT. This observation should be considered while designing treatment strategy and establishing justification of surgery for patients with CRC metastases to the liver.

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Radical resection after IORT containing multimodality treatment is most important determinant for outcome in patients treated for locally recurrent rectal cancer H. Rutten,* E. Dresen, M. Gosens, H. Martijn, A. Van den Brule, G. Creemers, G. Nieuwenhuijzen. *surgery, catharina hospital, Eindhoven, Netherlands.*

Introduction: Fortunately, the incidence of locally recurrent rectal cancer has decreased since introduction of total mesorectal excision in combination with (neo)-adjuvant treatment. However, if local recurrences occur, these are more difficult to treat. Prior surgery has severed the fascial borders of the rectal compartment, thus rendering a local recurrence a multicompartimental disease. Furthermore, prior radiotherapy used for the primary tumour limits tissue tolerance for reirradiation. Results of the multimodality treatment, consisting of neo-adjuvant radio (-chemotherapy), extended circumferential margin surgery and intraoperative radiotherapy, are presented. Methods: In a retrospective study 147 consecutive patients, who underwent surgery with curative intent, were analyzed. All patients received CT and/or MRI for staging of distant metastasis and local evaluation. In the early years 24 patients, who had irradiation as part of the primary treatment were not reirradiated. Later, reirradiation (30.6, 17 x 1.8Gy) was used. Full course (50.6 Gy, 25 x 1.8) and reirradiation was combined with chemotherapy in later years. Intraoperative radiotherapy was applied to the area of risk after resection of the tumour. Results: Median overall survival was 28 months (range 0-146). Five-year OS, DFS, and LC were 31.5, 34.1, and 54.1% respectively. For patients with a R0 resection, median OS was 59 months and the 5-year OS, DFS, and LC were 48.4%, 52.3%, and 68.9%. Patients who received re-irradiation or full course radiotherapy as part of the treatment of LRRC survived significantly longer (P=0.043) and longer without local recurrence (P=0.038) or metastasis (P<0.001) compared to patients who were not re-irradiated. Absence of nodal metastasis during the treatment of the primary tumor was associated with increased OS and MFS rates (P=0.008 and P=0.023, respectively). Conclusion: Neoadjuvant treatment helps to achieve a radical resection, which is the most important factor for outcome in locally recurrent rectal cancer patients. Nodal stage of the primary tumor is also associated with outcome.

univariate analysis outcome at 3 years

	No	%	% OS	p-value	% LC	p-value	% MFS	p-value
All patients	147		43.8		57.0		53.1	
Age								
younger than 60y	55	37.4	52.3	0.135	54.1	0.724	58.6	0.525
older than 60y	92	62.6	38.0		58.9		49.6	
Primary tumor stage								
I	17	11.6	80.1	**0.008**	57.7	0.599	85.7	**0.023**
II	66	46.3	46.9		54.2		54.3	
III	60	40.8	29.8		58.5		39.4	
Unknown	2	1.3						
Type primary surgery								
anterior resection	98	66.7	46.0	0.107	64.3	0.069	58.4	**0.007**
abdomino-perineal	44	30.0	37.9		40.7		38.9	
Interval to local recurrence								
less/equal 2y	68	46.3	48.7	0.782	57.9	0.917	60.6	0.221
more than 2y	79	53.7	40.1		55.9		47.8	
Symptoms								
no pain	87	59.2	48.5	0.118	67.0	0.086	57.0	0.162
pain	58	39.5	36.8		43.3		46.1	
unknown	2	1.3						
Dose EBRT								
0 Gy	24	16.3	25.0	**0.043**	37.6	**0.038**	17.8	**0.0001**
30.6 Gy (reirradiation)	57	38.8	47.6		48.9		58.7	
50.6 (full course)	66	44.9	49.3		69.0		61.2	
Type neo-adjuvant treatment								
no	24	16.3	25.0	0.082	37.6	0.114	17.8	**0.0001**
radiotherapy	36	24.5	47.6		64.3		59.4	
radiochemotherapy	87	59.2	49.3		58.5		62.5	
Type surgery								
LAR	28	17.7	65.1	**0.013**	80.4	0.055	66.2	0.175
extended	121	82.3	39.4		51.4		50.0	
Radicality								
R0	84	57.2	58.7	**0.0001**	74.9	**0.0001**	71.6	**0.0001**
R1	34	23.1	26.5		29.2		30.6	
R2	29	19.7	24.1		28.5		18.8	
Gender								
male	84	57.1	46.5	0.822	56.7	0.636	54.8	0.332
female	63	42.9	40.3		59.4		51.3	

OS: overall survival; LC: local control; MFS: metastasis free survival. LAR: low anterior resection

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Outcomes after esophagectomy for pT1 adenocarcinoma A.K. Saha,* C. Sutton, H.M. Sue-Ling, S.P. Dexter, A.I. Sarela. *Department of General Surgery, The General Infirmary at Leeds, Leeds, West Yorkshire, United Kingdom.*

INTRODUCTION This study examined the prevalence of lymph node metastasis and patterns of disease recurrence for patients with pT1 esophageal adenocarcinoma. METHODS From January 2000-December 2006, 44 patients had pT1 esophageal adenocarcinoma with pre-operative diagnosis of HGD or T1/T2 and N0 adenocarcinoma. Pre-operative staging comprised spiral, computed tomography scanning of the neck, thorax and abdomen and endoscopic ultrasound (EUS). No patients had neo-adjuvant treatment. 24 patients had an Ivor Lewis operation, 4 had an open transhiatal and 16 had a laparoscopic transhiatal operation. Pathological staging was standardized, with application of India ink to the outside of the entire, unopened specimen and transverse sections at 5-10mm intervals. RESULTS There were 37 men. The median age was 64 years (range, 35-80). 36 patients (82%) were on a Barrett's surveillance program. EUS staging was T0(2 patients, 5%), T1(10, 23%) or T2(32,72%). The median lymph node yield was 19 (3-51). Two patients (4%) had 0-6 nodes harvested, 11 patients (25%) had 7-12 nodes, 9 patients (21%) had 13-17 nodes and 22 patients (50%) had ≥18 nodes. There was no R1 resection. Four patients (9%) had poorly differentiated tumors and two patients (5%) had vascular invasion. Two patients (5%) had N1 disease; one patient had 1 metastatic node (no adjuvant treatment) and one patient had 3 metastatic nodes (adjuvant chemotherapy). Estimated survival (Kaplan-Meier) at 1 year and 3 years was 94% and

88%, respectively. Alive patients had median follow-up of 36 months (5 – 87). Two patients (8%) with N0 disease and 1 patient with N1 disease developed recurrent disease. The second patient with N1 disease is alive and well at 14 months. Three of the 4 patients with poorly differentiated disease developed recurrence; the 1 remaining patient is alive and well at 16 months. All patients with recurrence were treated with systemic 5FU and cisplatin. CONCLUSIONS pT1 esophageal adenocarcinoma was associated with a 5% prevalence of N1 disease. 7% of patients died of recurrent disease within 2 years of esophagectomy. 8% of patients with N0 disease developed recurrence. Poorly differentiated pT1 disease appeared to be at high risk for recurrence.

Characteristics of patients with recurrence

	N category	Depth of invasion	Node yield	Vascular invasion	Differentiation	Site of recurrence	Time to recurrence (months)	Time to death (months)
Patient 1	N0	Submucosal	19	V0	Poor	Mediastinal lymph nodes	6	7
Patient 2	N1 (1 metastatic node; no adjuvant treatment)	Submucosal	25	V0	Poor	Liver	8	14
Patient 3	N0	Mucosal	20	V1	Poor	Liver	22	24

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Attempted Salvage Resection for Recurrent Gastric or Gastroesophageal Cancer B. Badgwell,* J. Yao, B. Feig, P. Pisters, P. Mansfield. *UT MD Anderson Cancer Center, Houston, TX.*

Background: The outcome for patients with recurrent gastric or gastroesophageal (GGEJ) cancer is dismal and the effectiveness of treatment strategies for recurrent disease (RD) is not clear. The purpose of this study was to determine the outcome of surgery for RD. Methods: We reviewed records from 7,459 patients presenting at our institution from 1973 through 2005 with GGEJ cancer to identify those for whom resection of RD had been attempted. Overall survival (OS) was defined as time from surgery for recurrence to death or last follow-up and estimated by Kaplan Meier analysis. Associations between various clinicopathologic factors and curative resection were assessed with logistic regression, and differences in OS were tested with the Cox proportional hazards model. Results: Sixty patients underwent surgery for RD, 15 (27%) of whom had had positive margins after initial resection. Symptoms suggestive of RD occurred in 45 patients (75%) and RD was detected by endoscopy in 42 cases (70%). Fifteen patients received radiation and/or chemotherapy for recurrence prior to an attempt at re-resection. In 27 cases RD was unresectable at exploration. Of the 33 resected patients, 14 required concomitant resection of adjacent organs and 6 required colonic or jejunal interposition grafting. Three- and five-year OS rates for all 60 patients were 21% and 12%; median follow-up time for living patients was 23 months. Median OS for patients undergoing resection was 26 months vs. 6 months for those found to have unresectable disease at laparotomy ($P < 0.001$). Radiation and/or chemotherapy treatment prior to resection of recurrence did not correlate with resectability ($P = 0.8$) or OS ($P = 0.5$). Conclusion: Resection of recurrent GGEJ cancer is uncommon. However, significant survival can be achieved with resection but often requires adjacent organ resection or interposition graft placement.

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Hepatic Artery Infusion is a survival enhancing strategy in surgical therapy of Hepatic Metastases from Colorectal Cancer Kim Varker, MD

Charu Taneja, MD, FACS Giovanni Begossi, MD
Harold Wanebo, MD, FACS K. Varker,[1]* G. Begossi,[2] C. Taneja,[3] H.J. Wanebo.[4] *1. Ohio State University Medical Center, Columbus, OH; 2. Univ. Massachussetts Medical Center, Worcester, MA; 3. Roger Williams Medical Center, Providence, RI; 4. Surgical Oncology, Landmark Medical Center, Woonsocket, RI.*

Objective: Although resection is the gold standard in the treatment of liver metastases from colorectal cancer (CRC) most patients are unfortunately unresectable. The purpose of the study was to assess the role of hepatic arterial infusion in the management of these patients. Methods: Our clinical series included 274 patients (pts) with liver metastases from (CRC) (period 1978-2001). One hundred thirty four pts were treated surgically as follows: resection (87 pts), hepatic artery infusion (HAI) (30 pts), resection plus HAI (13 pts), and ablation plus HAI (8 pts). The remaining 139 pts received systemic therapy treatment. A separate (historic) group had supportive care only. Overall and median survival was measured by Kaplan-Meier method from treatment of liver metastases in the surgical group and from diagnosis in systemic therapy/historic groups. RESULTS: Resection had an overall 5 year and (median) survival of 25%(35months) which was enhanced by addition of adjuvant therapy with HAI(55% and median not reached). In the event of non-resectability, HAI with tumor ablation or HAI alone was associated with a median survival of 29 and 17 months respectively.Many of these patients had progressed on previous systemic chemotherapy(including FOLFOX).CONCLUDE:HAI provides valuable palliation for patients with nonresectable hepatic metastases (including chemo failure) and may extend tumor control in patients with resected high risk metastases.

Results: SURVIVAL OUTCOME-COLORECTAL HEPATIC METASTASES

Group	Pts. n	Surgical Intent	2 yr Survival	5 yr Survival	Median (mo) Survival
Resection only	87	Curative	73%	25%	35
Resection & HAI	13	Curative	66%	55%	not reached
HAI	30	Palliative	23%	0%	17
Ablation plus HAI	8	Palliative	57%	12.5%	29
Systemic Therapy	139	Palliative	13%	1%	11
Historic Controls	136	Supportive	8%	0%	6

Survival=Overall Survival

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Gemcitabine Resistance in Cultured Pancreatic Tumor Cells is Associated with Downregulation of PTEN and Activation of FAK M.P. Kim,[1]* A.N. Shah,[1] G.E. Gallick.[2] *1. University of Texas MD Anderson Cancer Center, Department of Surgical Oncology, Houston, TX; 2. University of Texas MD Anderson Cancer Center, Department of Cancer Biology, Houston, TX.*

Introduction: Gemcitabine is currently the standard chemotherapeutic for patients with advanced pancreatic cancer. The efficacy of gemcitabine therapy in pancreatic cancer remains limited due largely to the rapid development of tumor cell resistance through unknown mechanisms. Utilizing two gemcitabine resistant pancreatic cancer cell lines, the purpose of this study was to 1)characterize the morphologic and biochemical effects of gemcitabine on pancreatic cancer cells and 2)characterize the molecular mechanisms of acquired gemcitabine resistance. Methods: Two parental cell lines, ASPC-1 and L3.6pl, were maintained in increasing concentrations of gemcitabine until remaining cells demonstrated stable resistance. Differential expression and phosphorylation of Focal Adhesion Kinase(FAK) and the Src/FAK substrate p130CAS were examined by western blot analysis in L3.6 parental and resistant cell lines. PTEN expression was examined by western blot analysis in both L3.6 cell lines. Results:In response to persistent gemcitabine exposure, both resistant cell lines demonstrated morphologic and biochemical properties of Epidermal to Mesenchymal Transition(EMT), including increased migration. Western blot analysis demonstrated that tyrosine phosphorylation of focal adhesion kinase, an important regulator of migration, and phosphorylation of the Src/FAK substrate p130CAS were increased >2 fold in L3.6 resistant cells relative to parental cells. We recently found both resistant pancreatic cancer cell lines to express increased markers of pancreatic stem cells, including CD44, CD133, and ESA. Expression of the self-renewal gene PTEN was decreased >2 fold in L3.6p1 resistant cells relative to parental cells. Conclusions: Our results suggest that PTEN may serve a role in stem cell renewal and the activation of pro-migration pathways in gemcitabine resistant pancreatic cancer cells. The down-regulation of PTEN and activation of FAK and its downstream effector p130CAS may be important in EMT and acquired resistance to gemcitabine. Further evaluation of PTEN regulation and the FAK signaling pathway are necessary to establish specific roles in resistant cells.

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Justify aggressive multivisceral resection for primary locally advanced colon cancer? P. Luna,* M. Ramirez-Ramirez, S. Rodriguez-Ramirez, M. Gutierrez, A. Cravioto, H. Martinez, S. Labastida. *Surgical Oncology, Instituto Mexicano del Seguro Social, México D.F, Distrito Federal, Mexico.*

Background. Approximately 5-10% of all patients with colon cancer have locally advanced disease infiltrating neighboring organs requiring en bloc multivisceral resection. There is lack of appropriate information about treatment results and prognostic factors associated with morbidity and cancer death. Objective. To analyze the treatment results and to identify risk factors affecting morbidity and disease-free survival. Materials and methods. Retrospective analysis was performed. 5-year survival was obtained with Kaplan-Meier curves and compared with the Log-rank method. Logistic regression analysis and Cox proportional hazard model were performed to find risk factors of morbidity and cancer death. Results. From January, 2000 to December 2006, 820 patients with primary colon cancer were surgically treated at our institution. Forty males and 38 females required multivisceral colon resection. Primary colon tumor location was as follows: right, 25; transverse, 11; left, 14, and sigmoid, 28. Number of required anastomosis were: 0= 4; 1= 28; 2= 29; 3= 14, and >4= 3. 14 patients (17.9%) developed surgical complications and one operative death occurred (1.2%). Risk factors for postoperative morbidity were: diabetes mellitus, platelets > 400, 000, albumin < 3.5 g/dL, and blood transfusion (p= 0.009, 0.02, 0.001 and 0.001, respectively). Microscopic tumor infiltration was demonstrated in 51 patients (65.4%). Tumors staged were: T3,N0=10; T3,N1-2= 10; T4, N0= 31; T4, N1-2= 18, and T3-4, NX= 9. 48 patients received adjuvant chemotherapy. Median follow-up was 30.5 months. Local, distant or both recurrences were: 9%, 11.5%, and 3.8%, respectively. Five-year disease free survival was 71%. For those with N0, N+ and NX was 85%, 57%, and 50% (p=0.01). Identified risk factors for cancer related deaths were: number of resected organs and metastatic lymph nodes (p= 0.0001 and 0.01, respectively). Conclusions. Aggressive multivisceral surgical resection can be achieved with low morbidity and mortality. Furthermore excellent local control and disease-free survival rate.

Number of resected organs or structures

Organs	Patients (n)
1	14
2	14
3	22
4	14
5	14
Total	78

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Duodenal Gastrointestinal Stromal Tumors: A Diagnostic and Surgical Challenge M. Alassas,* E.S. Ong, J.M. Kane, J. Gibbs. *Roswell Park Cancer Institute, Buffalo, NY.*

Background: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the GI tract, but only 10-20% occur in the duodenum. This critical location can make diagnosis difficult and may require a more extensive resection than would be necessary for a non-duodenal GIST. Therefore, we examined the presentation and management of duodenal GIST, including the outcome following local excision (LE) versus pancreaticoduodenectomy (PD). Methods: Retrospective review of all primary duodenal GIST treated at a single institution from 1997-2007. Clinical presentation, tumor features, surgical procedure (LE vs PD), complications, and outcome were evaluated. Median follow up was 30 months. Student's t-test was used to compare disease-free survival (DFS) and overall survival (OS). Statistical significance was $p<0.05$. Results: Eleven patients were identified with duodenal GIST. Median age was 63 years and 64% were male. Presenting symptoms were GI bleeding (64%), abdominal mass (18%), and obstruction (9%). At least two diagnostic modalities (CT scan, colonoscopy, or esophagogastroduodenoscopy) were necessary to make the diagnosis in 64%. The tumor involved the second, third and fourth part of the duodenum in 63.6%, 45.5%, and 27.3%, respectively. Neoadjuvant and adjuvant therapy were administered in 16% PD and 40% LE. Six patients underwent PD with 20% morbidity. Five patients underwent LE with 0% morbidity. There was no perioperative mortality. Median tumor size was 8.5 cm (2-19 cm) for PD vs 4.5 cm (2-8 cm) for LE. Recurrence patterns were 27% liver only and 9% liver/peritoneum. Median DFS was 23 months for PD vs 30 months for LE (p=0.62). Median OS was 35 months for PD vs 30 months for LE (p=0.92). Conclusions: Despite significant symptoms at presentation, duodenal GIST can be difficult to diagnose. Given the limited margins necessary for adequate resection of a GIST, LE appears to be a reasonable option for duodenal tumors of the appropriate size and location. Duodenal GIST is associated with a high risk for tumor related death.

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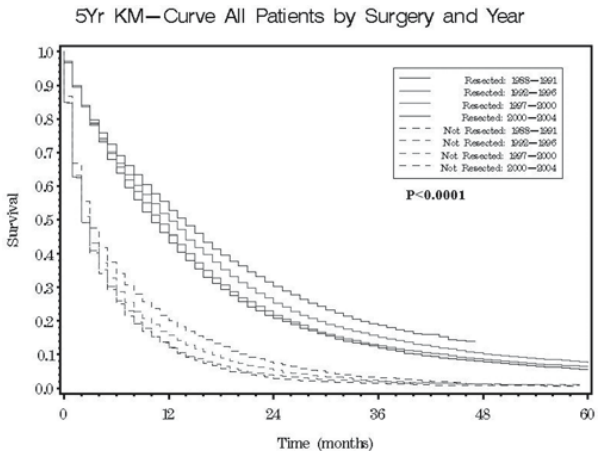
Trends in surgical management of stage IV colorectal cancer 1988-2004 E.S. Ong,* J. Wernberg, M.M. Alassas, T. Mashtare, G. Wilding, A. Rajput, M. Fakih, K. Bullard Dunn. *Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: Historically, surgery to remove the primary tumor has been recommended for patients with metastatic colorectal cancer. Recently, this practice has been called into question. We reviewed trends in surgical management and outcomes in patients with stage IV colorectal cancer. Methods: We queried the Surveillance, Epidemiology, and End Results (SEER) database to identify patients diagnosed with stage IV colorectal cancer between 1988 and 2004. Information on age at diagnosis, race, gender, surgery (resected vs. not resected), location (colon vs. rectum), and year of diagnosis were evaluated. Kaplan-Meier methods were used to estimate survival distributions. The log-rank test was used for comparison of survival distributions. A Cox proportional hazards model was used to study the effects of surgery, location, and the interaction between surgery and location adjusted for age at diagnosis, gender, race, and year of diagnosis. Statistical analysis and plots were done using SAS statistical software, version 9.1. Results: A total of 60,532 patients were identified. Cancers of the colon represented 85% of the patients with the remaining 15% being rectal tumors. The rate of surgical resection decreased by approximately 10% over the study period, but survival improved. (graph) Patients who underwent resection had a better overall median survival compared to those who did not (12 months vs. 3 months, $p<0.0001$). Interestingly, when location of the primary tumor was compared, patients who underwent surgery for rectal cancer were more than twice as likely to survive as patients with colon cancer (HR=2.22; 95% CI 2.06-2.38). Conclusion: The rate of resection in stage IV colorectal cancer decreased from 1988 to 2004, yet survival has improved. Nevertheless, patients who had surgery had better outcome than those who did not. Patients with rectal cancer in particular appear to benefit the most. These data suggest that surgical resection still may have an important role in treating metastatic colorectal cancer.



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High predictive value of pancreatic protocol CT as the only preoperative staging in pancreatic cancer R.M. Cisco,[1]* R.B. Jeffrey,[2] R.S. Greco,[1] J.A. Norton.[1] *1. Department of Surgery, Stanford University School of Medicine, Stanford, CA; 2. Department of Radiology, Stanford University School of Medicine, Stanford, CA.*

Background: In previous series, CT and other imaging studies have failed to adequately predict operability of pancreatic cancer. We have developed a new pancreatic protocol CT and have used it prospectively to assess operability in patients with pancreatic adenocarcinoma. **Methods:** From March 2005 to June 2007, 744 patients underwent pancreatic protocol CT using multiphasic technique with 3D reconstruction and curved planar reformations. Review of these studies identified 138 (18%) associated with new diagnosis of pancreatic adenocarcinoma. CT evaluation of resectability was compared with surgical and pathologic findings for the 42 patients who underwent attempted resection. CT criteria for resectability were absence of distant metastasis, absence of invasion of adjacent organs other than duodenum, and<50% circumferential contact of tumor with the celiac, hepatic and superior mesenteric arteries and portal and superior mesenteric veins. **Results:** On pancreatic protocol CT, 90 (65%) of 138 newly diagnosed patients were felt to have unresectable disease, while 48 (35%) were deemed to have resectable tumors. 10 of these 48 patients either refused surgery or had surgery elsewhere. 38 patients had surgery following a CT indicating resectability. Of these, 33 were resected, yielding a positive predictive value for resectability of 87%. SMV invasion was the cause of inoperability in all 5 patients incorrectly identified as operable on CT. Only 4 (4.5%) of 90 patients underwent attempted resection following a CT predicting unresectability. Resection was possible in just one of these cases, and that patient had positive margins. Therefore the overall accuracy of CT among patients undergoing surgery was 36/42 or 86%. **Conclusions:** A dedicated pancreatic protocol CT is the most valuable preoperative study for determining operability of pancreatic adenocarcinoma. Since inoperability in this series was due to SMV invasion rather than occult metastatic disease, diagnostic laparoscopy would add little utility.

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Tumor Differentiation and Extrapancreatic Invasion are More Predictive of Survival than the TNM System in Resected Pancreatic Cancer J. Helm, B.A. Centeno, M. Melis,* J. Farma, M.P. Malafa. *Division of GI Oncology, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.*

INTRODUCTION: Our analysis of the prognostic value of the AJCC (6th edition) stage groups after curative pancreatectomy for cancer revealed that the survival curves for groups stages IB, IIA, and IIB did not differ. Since histopathologic characteristics have been implicated in pancreatic cancer prognosis, we investigated the potential for these markers to improve upon the TNM system. METHODS: 138 consecutive patients who underwent pancreatectomy for ductal adenocarcinoma with curative intent (AJCC TNM stage IA – IIB) were studied. Review of charts, cancer registry, and the Social Security Death Index were used to determine treatment and survival, while an expert pancreatic pathologist reviewed the histology. RESULTS: Median survival was 21.4 months, with 1-, 3-, and 5-yr survival rates of 70%, 37%, and 33%, respectively. Histopathologic variables that diminished survival on univariate Kaplan-Meier analysis included local extrapancreatic invasion, poorly-differentiated histology, and angiolymphatic invasion ($p < 0.05$). Survival was not worsened by nodal metastases, microscopically-positive resection margins or perineural invasion, nor was survival better in patients whose ductal cancer arose from an IPMN. Multivariable Cox proportional hazard modeling identified local invasion (T3) and poorly-differentiated histology as the only significant predictors of worsened survival, adjusting for other variables. Hazard ratios indicate that death with disease is twice as likely at any given time after surgery with either predictor alone. For well-to-moderately differentiated tumors, the Kaplan-Meier disease-specific probability of surviving 5 yr after resection was 52% if the cancer was confined to the pancreas (T1 and T2), and 27% if not (T3). If the tumor was poorly differentiated, few patients with local invasion (T3) survived more than 2 yr. Few poorly-differentiated cancers were confined to the pancreas (T1 and T2). CONCLUSION: Combining the readily-available histological parameters of tumor differentiation and extrapancreatic invasion can improve prediction of outcome in patients undergoing pancreatectomy for adenocarcinoma.

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Serum Protein Profiling To Predict Disease Burden and Outcome in Pancreatic Cancer D.R. Carpizo,[1]* L.X. Qin,[1] M.F. Brennan,[1] A. Lokshin,[2] P.J. Allen.[1] *1. Memorial Sloan Kettering, New York, NY; 2. University of Pittsburgh, Pittsburgh, PA.*

Background: Current imaging, endoscopy, and single biomarkers are limited in determining the preoperative stage in pancreas cancer. The aim of this study was to determine the feasibility and accuracy of serum multi-analyte protein profiling as a preoperative staging and prognostic tool. Methods: Serum was preoperatively obtained from 127 patients undergoing operation. Patients were stratified into low (LR) and high risk (HR) groups. LR patients survived at least 18 months (n=33). HR patients were not resected due to occult metastatic disease at laparoscopy (n=22). 55 proteins were measured using multiplex assays (Luminex) previously developed for pancreatic cancer. Protein levels were log2 transformed. Differential expression was compared between groups by Wilcoxon rank sum test (WRS). Sample classification was performed (K-nearest neighbor) and repeated cross-validation used to determine tuning parameters and estimate classification accuracy. Results: Median survival was 28 and 9.2 months for LR and HR groups respectively. WRS test revealed 6/55 proteins differentially expressed ($p<0.05$). These proteins were MIP1b, CA-125, CA-72-4, CK-19, EGFR, and IL6R. Sample classification with 15 neighbors using 12 proteins produced an accuracy of 65%. This accuracy was increased to 75% when the LR group was limited lymph node negative patients who survived ≥18 months (7 nearest neighbors and 52 proteins). Differential expression analysis using this LR group identified seven proteins (Eotaxin, CK-19, CA 72-4, CA-125, ACTH, IL-6R, and MMP-9, Figure 1). Conclusions: Serum protein profiling can be used to distinguish patients with occult metastatic disease from patients with resectable cancers with an accuracy between 65-75%. Further development of serum protein profiling as a preoperative tool may assist in the assessment of disease burden and also predict outcome.

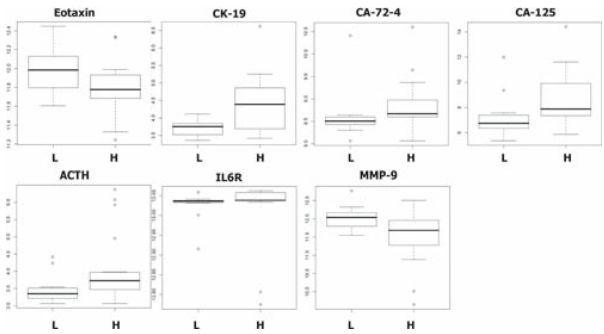

Figure 1: Differential Expression of log2 transformed protein levels of low risk (L n=12, lymph node negative) versus high risk (H n=21). Wilcoxon rank sum test for the median of each protein were as follows: Eotaxin p=0.044, Cytokeratin p=0.010, CA-72-4 p=0.026, CA-125 p=0.048, ACTH p=0.032, IL6R p=0.040, MMP9 p=0.18.

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Multimodal Management of Epithelial Hemangioendothelioma (EHE): A Single Institution Experience with Twenty-Five Cases J.S. Cardinal,* J.W. Marsh, M. DeVera, S. Holloway, J. Heckman, J. Steel, D.A. Geller, P. Fontes, A. Marcos, T.C. Gamblin. *Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Introduction: Epithelial hemangioendothelioma (EHE) is a rare vascular tumor of varying malignant potential. The course of the disease ranges from indolent to rapidly fulminant with few available prognostic factors. Treatment options for this rare tumor include liver resection, transplantation, and catheter based therapies. Methods: We performed a retrospective review of all patients with the diagnosis of EHE at our institution (1976-2007). We examined the treatment modality, overall survival, and treatment related complications. Results: 25 patients were diagnosed with EHE of which 12 were male (48%). 23 (92%) patients presented with bilobar disease. The median age at diagno-

sis was 38 years (range 9 months to 72 years). 19 patients underwent liver transplantation (LT) while 6 patients received transcatheter arterial chemoembolization (TACE) and 2 patients underwent hepatic resection. Two patients underwent combined therapy of TACE followed by LT. 12 patients either presented with or went on to develop extrahepatic disease. Mean overall survival was 167 months. Mean overall survival of LT patients was 172 months (range 16-256; 95% confidence interval 124-220). Patients receiving TACE or hepatic resection had mean survivals of 83 (range 18-101; 95% C.I. 54-112) and 39 months (range 13-68), respectively. Patients receiving TACE followed by LT had a median survival of 53 months (range 18-108; 95% C.I. 0-118). There was no difference in overall survival among groups. Treatment related complications occurred in 28% of cases and included primary nonfunction of allograft, biliary stricture, bile leak, hemorrhage, wound infection and septic complications. The extent of disease in the liver, presence of metastatic disease at the time of diagnosis, progression of disease from the time of diagnosis, or presence of angiolymphatic invasion failed to predict outcome. Conclusions: EHE is a rare tumor with an unpredictable clinical course. Treatment includes resection, LT and TACE. Survival was similar for all modalities in our series which represents the largest single institution experience to address the management of this rare tumor.

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Treatment of Peritoneal Carcinomatosis from the GI tract with a tumor suppressor gene product (hARF) delivered by peritoneal injection of adenoviral vector B. Rajeshkumar, S. Grossman, S. Paliwal, R. Kovi, G.F. Whalen.* *UMASS Medical School, Worcester, MA.*

Peritoneal carcinomatosis from cancers arising in the GI tract is a lethal clinical problem without adequate solution, even when the malignancy remains confined to the peritoneum. Since the peritoneal cavity is an enclosed space, local/regional therapy aimed at cells of epithelial origin might be useful treatment strategy. In this report we describe our experiments with a non replicating adenoviral vector that delivers a recombinant gene product to cancer cells growing on the surfaces of the peritoneal cavity. We have used human recombinant ARF (hARF), a gene which encodes a potent tumor suppressor protein that results in apoptosis of tumor cells via two separate mechanisms: negative regulation of P53 and interaction with C-Terminal Binding Protein. Innoculation of 3 million human colon cancer cells (Clone A) into the peritoneal cavity of nude mice reliably produced gross peritoneal implants and inanition by two months. In two separate sets of experiments, nude mice that had been innoculated with these cells were injected a week later with either: PBS (control), Ad-hARF (approximately 3 million viral particles in 0.5 ml PBS), Ad-LacZ (adenoviral vector control) [Experiment 1], or PBS (control), Ad-hARF (approximately 3 million viral particles in 0.5.ml PBS), Ad-hARF L50D (mutant ARF with an inactivating mutation for the C-Terminal Binding protein domain), Ad-LacZ (adenoviral vector control) [Experiment 2]. Mice were weighed, photographed and sacrificed two months after tumor innoculation. Ascitic fluid was collected and measured, the peritoneal cavity was opened and photographed, peritoneal implants were counted, scored and excised and weighed. Results from experiment 2 are representative. A single application of Ad-hARF into the peritoneal cavity of nude mice previously innoculated with human colon cancer cells produced an approximately 50% reduction of peritoneal tumor burden at two months. Delivery of gene products via adenoviral vectors to malignant epithelial cells in the peritoneal cavity may be a useful treatment strategy.

Experiment 2

	PBS	Ad-ARF	Ad-ARF L50D	LacZ
Body Wt gain/loss (gms)	0.79 ± 1.2	1.84 ± 4.1	3.27± 0.4	-0.83 ± 4.4
Tumor Wt (gms)	4.80 ± 0.6	1.03 ± 1.2	0.03 ± 0.1	4.10 ± 1.2
Ascites (ml)	2.5 ± 5.0	0	0	3.60 ± 0.6
Peritoneal cancer score	17 ± 8.9	11 ± 12	7.5 ± 9.5	25 ± 20.0

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Impact of adjuvant chemotherapy on survival for patients with Stage II colon cancer K.B. Stitzenberg,[1]* A. Stewart,[2] B. Palis,[2] K. Bilimoria,[2] B. Minsky,[3] E. Sigurdson.[1] *1. Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; 2. American College of Surgeons Commission on Cancer, Chicago, IL; 3. University of Chicago, Chicago, IL.*

INTRODUCTION: The utility of adjuvant chemotherapy for AJCC Stage II (T3/4N0M0) colon cancer is controversial. Most studies examining the role of chemotherapy in this population are small or constitute only subgroup analyses of larger adjuvant therapy trials. Despite several meta-analyses, the results have been varied. We seek to examine the impact of adjuvant chemotherapy on overall survival for a large national cohort of patients with Stage II colon cancer. METHODS: All surgically treated cases of Stage II colon cancer reported to the National Cancer Data Base by non-Federal hospitals from 1998 to 2000 were reviewed. Kaplan-Meier survival curves using log rank pairwise comparisons and Cox proportional hazards models were examined. RESULTS: Of the 59,285 cases of reported Stage II colon cancer, 19.7% received adjuvant chemotherapy (ACT): T3 18.6% (n=54,076), T4 30.2% (n=5209). 5-year overall survival (OS) for patients with T3N0M0 tumors receiving ACT was 79.5% compared to only 57.8% for patients receiving surgery alone ($p<0.0001$). For patients with T4N0M0 tumors, 5-year OS was 63.8% (ACT) and 37.0% (surgery alone) ($p<0.0001$). Controlling for patient age, surgical margins, extent of regional lymph node examination, tumor grade, and T stage, patients receiving ACT had an almost 40% decreased risk of death within five years of diagnosis (HR=0.609, 95%CI: 0.576-0.641) when compared to patients undergoing surgery alone. CONCLUSIONS: Some patients with Stage II colon cancer do benefit from adjuvant chemotherapy. Chemotherapy should be discussed as a treatment option with these patients. As new chemotherapeutic agents become available, research efforts should be focused on identifying those patients with Stage II colon cancer who are most likely to benefit from adjuvant chemotherapy.

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Tumor status after neoadjuvant chemoradiation allows alterations in decisions regarding sphincter preservation for rectal cancer E.B. Valsdottir,* J.H. Marks, S.S. Yarandi, D.A. Newman, G.J. Marks. *Lankenau Hospital and Institute of Medical Research, Wynnewood, PA.*

Introduction: Improved tumor downstaging and complete response rates of rectal cancer treated with neoadjuvant therapy have been observed. To extend sphincter preservation, decisions regarding the need for permanent colostomy can be based on the post- chemoradiated cancer. We evaluated long term oncologic outcome in T 2-3 rectal cancer patients in the distal 3 cm. Methods: From a prospective database, data regarding all T2 and T3 rectal cancers in the distal 3 cm of the rectum undergoing curative resection between 1/98 and 12/04 were evaluated. All were treated with neoadjuvant chemoradiation (CXRT). Median dose of XRT was 5400 cGy (4500-7560 cGy). Chemotherapy was 5FU based. Surgery was performed between 8-12 weeks following completion of treatment (mean 8.9 weeks/4-17 weeks). Only patients with fixed cancers after treatment underwent APR (N=5). Oncologic outcomes of patients undergone sphincter preservation surgery were analyzed (N=77; 94%). Results: Of the 77 patients, 52 were men and the mean age was 60.7 years (22 - 85 y.o.). An APR would be required in 100% of these patients based on pretreatment presentation. Response to neoadjuvant therapy was deemed good to complete in 55 patients (71%). Surgery included proctosigmoidectomy with hand-sewn coloanal anastomosis (n=58), stapled colo-anal (n=2) and transanal endoscopic microsurgery (n=17). CR rate was 22%. There was 1 positive margin (disease free at 77 months). No patient was lost to follow up. With a mean follow up of 55.4 months (2.1-114.4), local recurrence rate was 2.6%. KM5YAS was 86%, 90% in the node negative patients and 78% in the node positive patients ($p=0.001$). Sphincter preservation was ultimately successful in 70 patients (91%). Conclusion: Tumor status after neoadjuvant chemoradiation allows alterations in decisions regarding sphincter preservation for rectal cancer in the distal 3 cm of the rectum with excellent long term oncologic outcomes.

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Is Survival After Pancreatectomy For Adenocarcinoma Impacted By Performance Status? J. Mullinax,* S. Al-Saadi, D. Villadolid, M. Vogt, S.M. Cowgill, S. Goldin, A.S. Rosemurgy. *Surgery, University of South Florida, Tampa, FL.*

INTRODUCTION: Survival after pancreatectomy for adenocarcinoma is poor. While many factors impact survival after pancreatectomy, intuitively, patients with the best performance status have the best prognosis. As well, performance status after resection may impact choice of adjuvant therapy or enrollment into treatment protocols. This study was undertaken to determine the independent impact of performance status after pancreatectomy on survival. METHODS: Patients with a Karnofsky Performance Status (KPS) > 60 after pancreatectomy for adenocarcinoma were enrolled into a placebo-controlled prospective randomized adjuvant therapy trial. For 96 patients randomized to receive placebo, the impact of KPS at 6 weeks after pancreatectomy (i.e., protocol initiation) on survival was determined utilizing Cox Proportional-Hazards regression and Log-rank test. Patients were followed for 24 months after the last patient was enrolled into the trial. Data are presented as median, mean +/- SD, where appropriate. RESULTS: Median patient age was 65 years (range 38 to 83 years); 48% of the patients were male. Resections were R0 for 66% and R1 for 33% of the patients. AJCC Stage was IA for 9%, IB for 21%, IIA for 11%, and IIB for 56% of the patients. Overall survival was 12 months, 19 months +/- 14.3, with 35% of patients alive at 24 months. KPS after pancreatectomy did not correlate with survival by regression analysis or by survival curve analyses when patients were stratified by KPS (p=NS) (Table). CONCLUSIONS: For patients with adenocarcinoma undergoing pancreatectomy without adjuvant therapy, survival is poor. While, intuitively, healthiest patients have the best prospects for prolonged survival, performance status (i.e., KPS ≥ 60) after pancreatectomy is not related to and does not independently impact survival. Since performance status does not impact survival after pancreatectomy for adenocarcinoma and since patients undergoing pancreatectomy for adenocarcinoma generally succumb to recurrent cancer, performance status seems not to impact the biological behavior of pancreatic cancer following resection.

KPS After Pancreatectomy	% Alive at 24 months	Survival (months)
100	42%	19, 22 ± 15.1
90	37%	11, 19 ± 15.3
80	18%	9, 15 ± 12.3
70	38%	19, 19 ± 13.7
60	50%	20, 20 ± 13.6

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Impact of surgeon and hospital factors on the surgical treatment of locally advanced colon cancer: A population-based study A. Govindarajan,[1]* A. Kiss,[3] L. Rabeneck,[3] A.J. Smith,[1] D. Hodgson,[2] C.H. Law.[1] *1. Division of General Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; 2. Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; 3. Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada.*

INTRODUCTION: Despite current guidelines, only approximately one-third of patients in the United States with locally advanced colorectal cancer (LACRC) are treated with multivisceral resection (MVR). In this population-based study, we evaluated surgeon and hospital factors associated with the use of MVR. METHODS: Patients ≥66 years of age who were diagnosed with non-metastatic, locally advanced colon cancer from 1991-2002 were identified from the Surveillance, Epidemiology and End Results-Medicare database. Hierarchical multivariable models were used to examine the independent effect of surgeon and hospital factors (case volumes, specialization) on the type of surgery performed (MVR versus standard resection) and on overall survival. RESULTS: Overall, 2935 patients met study criteria, with MVR being performed in 31% of patients. In adjusted analysis, hospital volume was significantly associated with MVR, with hospitals in the highest volume quartile being 33% more likely to perform MVR than hospitals in the lowest volume quartile. In contrast, surgeons in the lowest volume quartile were 25% more likely than surgeons in the highest volume quartile to perform MVR. Patients treated at a designated cancer centre were significantly more likely to receive MVR than patients treated at non-cancer hospitals (OR: 2.14, p=0.038). Analysis of individual providers found that 40% of surgeons and 25% of hospitals did not perform MVR on any of their LACRC patients. Treatment at a high-volume hospital or at a cancer centre were also associated with significantly improved overall survival. CONCLUSIONS: Patients with LACRC were more likely to receive MVR when treated at a high-volume hospital or at a cancer centre, whereas treatment by a high-volume surgeon was paradoxically associated with decreased performance of MVR. A substantial fraction of surgeons did not perform MVR on any of their LACRC patients suggesting that beliefs of individual surgeons may be most relevant in the type of treatment patients receive.

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Methylation-Induced Silencing of TFPI-2 is an Early-Stage Event in Colorectal Cancer N. Ahuja,[1]* S. Glockner,[1] K. Schuebel,[1] L. Van Neste,[2] M. Van Engeland,[3] M. Dhir,[1] K. McGarvey,[1] S. Baylin.[1] *1. Surgery, Johns Hopkins University, Baltimore, MD; 2. Ghent University, Ghent, Belgium; 3. University of Maastricht, Maastricht, Belgium.*

Introduction: Tissue factor pathway inhibitor (TFPI-2),a Kunitz-type serine proteinase inhibitor may inhibit tumor metastasis by preventing degradation of the matrix. Aberrant TFPI-2 methylation is a possible mechanism for loss of TFPI-2 expression in pancreatic and hepatocellular cancer. We have now investigated the status of TFPI-2 methylation in colorectal cancer (CRC). Methods: CRC cell lines were treated with demethylating drug, 5μM 5aza-deoxycytidine(DAC) for 96 hours or a histone deacteylase inhibitor, 300nM Trichostatin A(TSA) for 18 hours. Total RNA was harvested, labeled, hybridized, and processed on Agilent microarray. Methylation and expression status was investigated by methylation-specific PCR (MSP) and RT-PCR, respectively. Results: We used a microarray-based gene expression screening approach to identify novel genes affected by aberrant DNA methylation in CRC cell lines. By comparing wild type HCT116 colon cancer cells with HCT116 DNMT1(-/-) DNMT3b(-/-) double knockout (DKO) cells, which have virtually complete loss of global 5-methylcytosine, as well as other CRC cell lines after DAC treatment, we identified TFPI-2 as a gene that is frequently upregulated in either genetically or pharmacologically demethylated CRC cell lines. We, next, determined the methylation patterns of TFPI-2 in colorectal neoplasms. Aberrant methylation of TFPI-2 was widespread in colorectal adenomas(55/56;97%) [serrated (16/17;94%), tubular(17/17;100%) and villous (22/22;100%)] and in CRC throughout all clinical stages(114/115; 99%), but rare in normal colon(1/37;3%). We, next, tested utility of TFPI-2 hypermethylation as a stool marker for early detection of CRC. In a blinded study of 56 patients, we detected methylated TFPI-2 alleles in 11/36 stool samples from patients with neoplastic colorectal lesions(sensitivity:30.6%), but in 2/23(8.7%)control patients(specificity 91.3%;p=0.06). Conclusion: TFPI-2 methylation is a frequent and early event in colorectal carcinogenesis. Methylation of TFPI-2 may be useful as a marker for early detection of colorectal neoplasms.

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Does Absence of Metastasis in the Regional Lymph Nodes represent a Specific Clinical Pattern for Patients with Synchronic Hepatic Metastasis from Colorectal Carcinoma? M. Gutierrez,* S. Rodriguez, S. Rojas, P. Luna-Perez. *Division de Cirugia, Hospital de Oncologia, Mexico City, DF, Mexico.*

Introduction Primary tumor regional positive lymph node invasion has been reported as a prognostic factor in resectable liver metastasis from colorectal cancer (CRC), although series mix synchronic and metachronic disease. Appropriate stratification for clinical studies testing new multimodal approaches for advanced CRC should be pursued to correctly compare between groups. The specific objective of this study was to evaluate the frequency and clinical pattern of the TxN0M1 subgroup of patients. Methods We performed a retrospective review of the clinical records of 193 consecutive patients with the diagnosis of stage IV CRC, treated at a Colorectal Service at a tertiary referral Oncology Hospital, between January 1995 and July 2000. Results 75 patients had resective surgery of the primary tumor, from the 193 patients with stage IV CRC initially identified. Sixteen cases (21%) had positive nodes (N+) in the specimen and 59 cases (79%) had no positive nodes detected: 16 cases (21%) were

technically negative (N0) (no positive nodes in 12 or more nodes examined) or 38 cases (52%) had no positive nodes in 7 or more nodes examined. The colorectal and hepatic resections were: low anterior (27), abdominoperineal (19), anterior (12), left hemicolectomy (7), right hemicolectomy (7), and multivisceral resection with part of the urinary bladder (3), bisegmentectomies (3; 2 in the N0M1 and 1 in the N+M1) and 2 lobectomies (both in the N0M1 group). Survival without evidence of disease was achieved in 3 patients with N0 disease (25%, average 257 days), and in 1 patient with N+ disease (6%, 230 days). Conclusion A significant group of the patients with synchronous hepatic metastasis of CRC have N0 in the resected primary tumor specimen with 12 or more nodes studied. The N0M1 subgroup showed clinical differences when compared with the N+M1 subgroup, differences that could represent a specific tumor biology. More specific attention for the TNM classification subgroups within stage IV of CRC should be put in retrospective and prospective analysis

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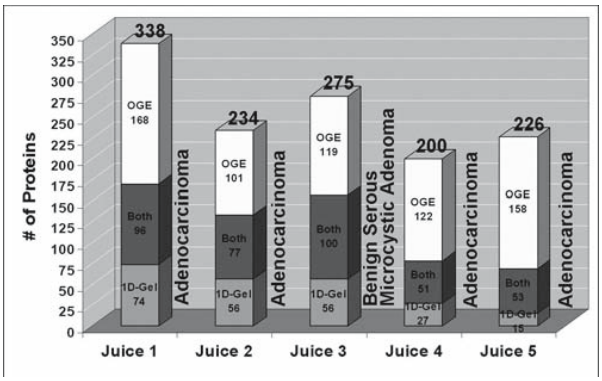
Comparative Proteomic Analysis to Identify Pancreatic Cancer Biomarker in Pancreatic Cancer Duct Fluid (Juice) using 1D-Gel, OFFGEL, and High Performance Liquid Chromatography-Chip-Mass Spectrometry Technology V. Bhat, R. Wiatrek,* A. Budke, C. Thompson, M. Shabahang, A. Rao, A. Asea. *Surgery, Texas A&M University/Scott and White, Temple, TX.*

Introduction: Pancreatic ductal adenocarcinoma is the 4th leading cause of cancer death in USA and has the lowest survival rate for any solid tumor. Proteomic analysis of patient samples may provide a new diagnostic marker for pancreatic cancer. Pancreatic juice is an ideal proteomic sample that is rich in cancer-specific proteins, given its proximity to the tumor. Methods: This study prospectively analyzes pancreatic duct fluid samples collected intraoperatively during pancreatic resections for four cases of pancreatic adenocarcinoma and one case of pancreatic serous cystadenoma. Each sample is analyzed using HPLC-Chip-MS technology in a high throughput manner using Gel-LC-MS/MS and peptide OFFGEL Electrophoresis (OGE) followed by MS/MS. The collected data was then analyzed and semi-quantified with Spectrum Mill bioinformatics tool to identify potential protein biomarkers. Results: Over 600 non-redundant human proteins were identified in pancreatic juice with <1% false positive rate. Of these, ~100 proteins were found in common between multiple samples. A larger number of proteins were identified using OGE peptide fractionation than with the 1D-Gel protein separation method and combining these two methods yielded the highest number of proteins identified per sample. Semi-quantitative analysis based on spectrum intensity yielded ~60 proteins whose levels are changed >3 fold compared to the benign sample. Proteins from all functional classes, cellular localization and their relative abundance were identified using these methods. Conclusions: Many of the identified proteins are pancreatic cancer related and therefore could be potential candidates for diagnostic markers. To date, this is the first report showing more than 200 proteins in a single analysis of pancreatic duct fluid. Candidate pancreatic cancer-related proteins found in this study will be further validated in plasma, tumor interstitial fluid (TIF), and tumor tissue samples collected from the same patients during resection to continue the search for an ideal pancreatic cancer biomarker.



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The Association Of Hospital Volume With Rectal Cancer Surgery Outcomes E.A. Guzman,* C. Anderson, L. Bening, A. Pigazzi. *Surgery, City of Hope, Duarte, CA.*

INTRODUCTION: Hospital volume has been found to be a surrogate for improved outcomes in several surgical procedures. However, the relationship between hospital volume and surgical outcomes in rectal cancer patients has not been conclusively determined. The aim of this project is to analyze differences in surgical outcomes between high and low volume hospitals in patients with rectal cancer. METHODS: The Office of Statewide Health Planning and Development database (OSHPD) is a large database of all hospital discharges in the state of California that accrues both clinical and financial data. Data obtained form 2000 to 2005 was analyzed. High volume hospitals were defined as those that performed more than 10 rectal cancer resections per year. Only patients with a diagnosis of rectal cancer who underwent either low anterior or abdominoperineal resections were analyzed. Patients with colonic or rectosigmoid neoplasms where excluded. RESULTS: A total of 6459 rectal resections in 314 hospitals were identified. There were 19 high volume and 295 low volume hospitals. The median case volume over six years was 83 in high volume and 11 in low volume hospitals. Overall postoperative mortality was significantly lower in high volume hospitals (0.98% VS 1.69%)(OR 0.58, p<0.05). In-hospital complications were significantly lower in high volume centers (27% VS 32%)(OR 0.79, p<0.001). Also, high volume hospitals were significantly more likely to perform sphincter preserving surgery (64% Vs 54%)(OR 1.51, p<0.0001). CONCLUSION: Rectal cancer patients had lower morbidity and mortality rates; and higher chances of sphincter preserving surgery in high volume centers. This data argues for regionalization of surgical care in patients with rectal cancer.

Rectal Cancer Surgery Outcomes

	High Volume	Low Volume	p value
Mortality (%)	0.98	1.69	<0.05
Complications (%)	27	32	<0.001
Sphincter Preservation (%)	64	54	<0.0001

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Nodal Staging and Recurrence in Rectal Cancer Patients Undergoing Sentinel Lymph Node Mapping Technique Compared to Conventional Surgery S. Saha,[1]* N.C. Madugonde,[1] D. Iddings,[2] V. Karia,[1] M. Ghanem,[1] D. Wiese,[1] S. Kaushal,[1] B.K. Ganatra,[1] M. Arora,[1] T. Singh.[1] *1. Mclaren Regional Medical center, Flint, MI; 2. Genesys Regional Medical Center, Grand Blanc, MI.*

Introduction: Nodal status remains one of the most important prognostic factors in rectal cancer (R Ca). Sentinel lymph node (SLN) mapping (M) has been found to upstage more patients (pts) with nodal disease compared to conventional (conv) surgery (surg). Hence, a comparative study was undertaken in R Ca pts for nodal staging and recurrence in SLNM (group A) vs conv surg (group B). **Methods:** Group A (gpA) pts (n=75) underwent SLNM with 1% lymphazurin followed by standard oncologic resection including total mesorectal excision. Group B (gpB) pts (n=100) underwent conv surg by non-oncological surgeons. Pts with only locally invasive R Ca were included in the study. Data for age, T stage, nodal status, and recurrence were compared. Recurrence was calculated only for pts with minimum follow up of 12 months. Student t-test was used to determine statistical significance. **Results:** The 175 consecutive pts with R Ca that were studied had median age of 66.2 yrs (68 yrs for gpA and 66 yrs for gpB). For 75 gpA pts, SLNM was successful in 92% of cases with 2.2 SLNs/pt. All 6 pts with no identifiable SLNs underwent neoadjuvant (NeoAdj) treatment (Rx). For gpA pts, there were 11.5 LNs/pt vs 8.1 LNs/pt in gpB pts (p<0.01). NeoAdj Rx was received by 80% of gpA pts vs 39% of gpB pts. In spite of downstaging by NeoAdj Rx for more pts in gpA compared to gpB, overall nodal metastases were similar in both the groups (28.2% and 29.4% respectively; p<0.88). With a minimum follow up of 12 months and median follow up of >43 months, overall recurrence between 60 gpA pts vs 61 gpB pts was 10% and 27.8% respectively (p<0.013; Table 1). Specifically, in the node negative pts, the recurrence was significantly

lower in gpA pts compared to gpB pts (6.3% and 20% respectively; $p<0.05$; Table 1). **Conclusion:** Despite significant downstaging by higher use of NeoAdj Rx in SLNM pts, the SLNM technique resulted in identification of more nodes per specimen, adding to the staging accuracy. Even with longer median follow up, the truly node negative SLNM pts [pN0(i-)] had significantly lower recurrence compared to conv node –ve gpB pts (pN0).

Table 1: Recurrence by Nodal Status for Gp A (n=60) vs. Gp B (n=61) [10% and 27.8% respectively; $p<0.013$].

	Node +ve			Node -ve		
T Stage	Gp A (n=13)	Gp B (n=21)	*p* Value	Gp A (n=47) [pN0(i-ve)]	Gp B (n=40) [pN0]	*p* Value
T1	0	0		1	2	
T2	1	0		1	2	
T3	2	8		0	2	
T4	0	1		1	2	
Total(T1-T4)	3 23.0%)	9 42.8%)	<0.24	3 (6.3%)	8 20.0%)	<0.05

1. SLNM Grp (gpA)
2. Conventional Surgery Grp (gpB)
3. Minimum follow up of 12 months for both groups, with mean follow up of 52.1 months for gpA and 43.2 months for gpB.

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Survival From Metastatic Gastrointestinal Stromal Tumors in the Era of Imatinib A. Artinyan,* J. Kim, P. Soriano, J. Ellenhorn. *General Oncologic Surgery, City of Hope National Medical Center, Duarte, CA.*

Background: Metastatic gastrointestinal stromal tumors (GIST) are aggressive malignancies with poor clinical outcomes. In 2002, the Food and Drug Administration approved imatinib for the treatment of metastatic and unresectable GIST following the demonstration of significant partial response. Imatinib's effect on overall survival for metastatic GIST, however, has yet to be established. Methods: The Surveillance, Epidemiology, and End Results (SEER) registry was queried for all patients diagnosed with GIST between 1995 and 2004. Patients were categorized by year of diagnosis into two groups, 1995-2000 and 2001-2004, in order to evaluate the treatment effect of imatinib. Kaplan-Meier curves were constructed to assess differences in survival over time. Multivariate Cox-regression analysis was performed to determine trends in survival adjusted for other clinical and demographic factors. Results: Of 2467 patients with GIST identified between 1995 and 2004, 552 had metastatic disease. The overall median survival for patients with metastatic GIST was 23 months. Examination of survival in the 1995-2001 and 2001-2004 time groups revealed a significant increase in median survival from 12 to 33 months, respectively ($p<0.001$); 3-year overall survival increased from 24% to 48%, respectively ($p<0.001$). On multivariate analysis adjusting for age and surgical resection, diagnosis in the 2001-2004 period was a significant independent predictor for improved survival in patients with metastatic GIST (HR 0.45, 95% CI 0.35-0.58, $p<0.001$). Conclusions: Clinical outcomes for patients with metastatic GIST have improved significantly in the era of imatinib. Although the majority of patients still die of metastatic disease, imatinib has dramatically improved survival.

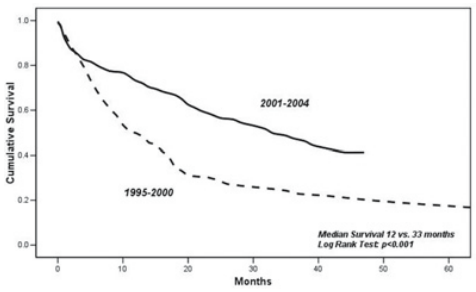

Figure 1: Comparison of survival by time period in patients with metastatic GIST.

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Variation in Lymph Node Count in Colorectal Cancer Resections is Unaffected by Surgeon, Specialty, Volume and Technique M. Choh,[2]* E. Esteben-Agusti,[1] J.M. Velasco,[1] T.J. Hieken.[3] *1. Surgery, Rush North Shore Medical Center, Skokie, IL; 2. Rush University Medical Center, Chicago, IL; 3. Rush Medical College, Chicago, IL.*

Introduction: Accurate detection of lymph node (LN) metastases in colorectal cancer patients is important for prognosis, determining the need for adjuvant therapy and an extensive lymphadenectomy may be therapeutic. Documentation of a minimum threshold number of LNs now is being used as an indicator of quality of care. Factors relating to the patient, surgeon and pathologist may influence LN count. We undertook this study to identify variables related to the number of LNs reported with colorectal cancer resections in our community teaching hospital. Methods: We retrospectively accessed our Cancer Registry data on 630 colorectal cancer cases. Data were confirmed by chart, pathology report and operative note review. Statistical analysis was performed using an SAS statistical software package. Results: Overall the mean number of LNs removed per case was 13.3±0.3 (median 12). We found that male patient gender ($p=0.01$), increasing age (decade of life, $p<0.01$), increasing comorbidities (cardiac, pulmonary, $p<0.01$), preoperative chemoradiotherapy ($p=0.001$), more distal tumor location ($p<0.0001$), earlier T stage ($p<0.0001$) and the individual pathologist (ranging from 6.1±1.4 to 17.5±1 mean LNs per case among 5 individuals, $p<0.0001$) were significantly associated with a lower number of LNs reported retrieved. Individual surgeon, surgeon volume, surgeon specialty training, surgical approach (laparoscopic or open), surgical intent (palliation or cure), tumor grade and preoperative CEA level were not significant. Conclusions: There are valid reasons for variation in LN count reported with colorectal cancer resections. In our study, lower LN yields were seen for males, older patients, those with comorbid illness, after preoperative chemoradiotherapy, with more distal and earlier tumors and varied with the individual pathologist, but not among surgeons. LN count was independent of surgeon specialty, volume or approach. Institutional awareness of the importance of LN counts may increase LN retrieval by pathologists. Reimbursement to surgeons and rating of surgeons based on LN count in their colorectal cancer specimens appears unwarranted.

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Zero leak and mortality rate for minimally invasive oncologic approach to esophagectomy in a high volume tertiary referral center C.A. Galanopoulos,* J. Jay, J.D. Linder, A. Vo, D.R. Jeyarajah. *surgery, methodist dallas medical center, Dallas, TX.*

Introduction: The use of a minimally invasive approach to esophageal surgery is being examined as a sound oncologic approach to the treatment of malignant and benign esophageal disease. We hypothesize that this approach is oncologicaly sound, with advantages over open esophagectomy, and is associated with a decrease in morbidity and mortality. Methods: This is a retrospective study at a high volume teaching institution, same surgeons (dedicated team consisting of a gastroenterologist, thoracic and HPB/GI surgeon), on the safety outcomes over the last 2 years (September 2005-2007) of 19 consecutive combined thoracoscopic and laparoscopic esophagectomy with cervical esophagogastrostomy. Operative time, blood loss, ICU stay, leak rates, nodal count, margin status, cell type, thirty day mortality rates, BMI, and use of a gastric conduit was evaluated. These results were then compared to historical open 3-field esophagectomy and laparoscopic esophagectomy data. Results: Of 37 esophagectomies, nineteen were considered minimally invasive (13m/6f). Average age and BMI were 61 and 27.2%. Median operative time and blood loss were 352 minutes and 300ml. Median ICU stays of 2 days. Anastomotic leak rate was 0%. Gastric conduit, cervical esophagogastrostomy, and pyloroplasty was used in all patients without preoperative gastric conditioning. One positive margin. 64.7% adenocarcinoma, 11..8% squamous cell carcinoma, 11.8% Barrett's with high grade dysplasia, 11.8% with achalasia. Median number of nodes was 10 (87.5% were N0). Mortality rate of 0%. Conclusion: This retrospective review suggests that a combined thoracoscopic and laparoscopic esophagectomy with cervical esophagogastrostomy approach by a dedicated surgical team at a high volume teaching institution is clinically safe and follows time honored oncologic principles. It was associated with improvements in leak and mortality rates and is comparable, and at times, exceeds historical criteria for safety.

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Epidural Anesthesia and Analgesia Has a Modest Effect on Clinical Outcomes Following Pancreatoduodenectomy D.X. Choi,* B. Domajnko, L.O. Schoeniger. *Surgery, University of Rochester, Rochester, NY.*

Background: Epidural anesthesia and analgesia (EAA) has demonstrated improved outcomes in certain surgical procedures. It has been employed during pancreatoduodenectomy (PD) in an attempt to reduce the associated significant post-operative morbidity and lengthy hospitalization. Despite the widespread use of epidural catheters, their utility in PD patients has not been studied previously. Methods: A retrospective chart review of 42 consecutive patients who underwent PD by a single surgeon at a high volume center was carried out. PD patients with and without EAA were compared. Endpoints included: operating-room delay, intraoperative blood loss, intravenous fluid requirements, intensive care unit (ICU) admission, pain score, resumption of bowel function, length of stay, morbidity, and mortality. Fisher's Exact Test was used for statistical analysis. Results: 18 of 42 patients received epidural catheters. Patients with epidurals: 1) reported less pain on post-op day 2 ($p=0.03$) but the pain was not significantly different at all other times, 2) were more likely to require ICU admission ($p=0.02$), and 3) required more frequent alteration of analgesic regimens ($p=0.0000001$). EAA patients had statistically non-significant increased intraoperative blood loss and perioperative fluid requirements. The study groups did not differ in regard to resumption of bowel function, need for total parenteral nutrition, length of hospital stay, or morbidity. Conclusions: In this clinical audit, EAA was not associated with clinical outcome benefits for patients undergoing PD. The study was able to identify a modest reduction in post-op pain that was limited to a single day. EAA patients were also more likely to have greater intraoperative blood loss and fluid requirements, and more likely to require ICU admission with the latter being statistically significant. EAA did not prevent any of the complications commonly encountered after PD: ileus, gastroparesis, or biliary and pancreatic leak.

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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colon cancer and peritoneal carcinomatosis G. Glockzin,* N. Ghali, H.J. Schlitt, P. Piso. *Department of Surgery, University of Regensburg Medical Center, Regensburg, Bavaria, Germany.*

Introduction: More than 10 % of the patients with colon cancer show peritoneal carcinomatosis at the time of initial diagnosis. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) represent an innovative therapeutic option for a highly selected part of these patients leding to prolonged survival rates. In the present study we evaluated morbidity, mortality and first follow-up data of 40 patients operated on for colon carcinoma with peritoneal metastases. Patients and methods: Between 2004 and 2007 more than 175 patients underwent cytoreductive surgery and HIPEC at the University of Regensburg Medical Center. Forty of these patients were operated on for colon cancer excluding rectal and appendiceal cancer. The mean age of patients at the time of surgery was 54 years. Seventeen patients were female (42.5 %) and 23 male (57.5 %). The mean follow-up time was 9,5 months. 1-year-survival was calculated for 20 patients according to the Kaplan Meier method. Results: Twenty-four patients underwent complete cytoreduction. Sixteen patients had residual tumor mass after surgery. The mean operative time was 211 minutes. Overall postoperative morbidity rate was 35 % decreasing from 45 % in the first 20 patients to 25 % in the last 20 patients. The leading postoperative complications were ileus (12.5 %), anastomotic leakage (10 %), abscess (5 %) and pulmonary embolism (5 %). There was no operative mortality in our series. The overall 1-year-survival was 75 % ($n = 20$). In patients with complete cytoreduction 1-year survival was 95 %. Conclusions: Cytoreductive surgery and HIPEC could be performed with low mortality and acceptable morbidty rate in specialized centers. Accurate pre-operative diagnostics and patient selection play a pivotal role for long-term patient outcome. Further prospective randomized trials are required for standardization of the treatment strategy including CRS and HIPEC in patients with colon carcinoma and peritoneal carcinomatosis.

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Anal human papilloma virus and dysplasia in HIV-negative women M. Kapadia,* L.G. Melstrom, D.J. Bentrem, A.L. Halverson. *Surgery, Northwestern University, Chicago, IL.*

Background: Human papilloma virus is a known risk factor for anal dysplasia. HIV-positive individuals and men who have sex with men are recognized high-risk groups for anal dysplasia. The frequency of anal dysplasia in HIV-negative women has not been well evaluated. In this study our purpose was to assess presenting symptoms, efficacy of treatment, risk factors for recurrence of condyloma and dysplasia in individuals treated for anal human papilloma virus. Methods: A retrospective review was conducted on 252 consecutive patients treated for anal HPV. Condyloma lesions and areas of leukoplakia were treated with excision and fulguration. The frequency of dysplasia and recurrence were compared with gender, HIV status, and burden of disease at initial presentation. Results: Two hundred twenty-nine patients were found to have anal condyloma with standard anoscopy. One hundred fifty-three individuals were referred for symptoms and 70 were referred for evaluation following an abnormal anal pap smear. In symptomatic patients, the most common presentation was the presence of a mass (54.2%), bleeding (45.6%), pain (27.5%) and itching (13.1%). Of individuals referred following an abnormal anal pap smear, 41(58.6%) had gross condyloma identified on initial anoscopy. The frequency of dysplasia was 30% in HIV-positive men and 22% in HIV-negative men. Dysplasia was present in 32% of women (all HIV-negative). Of the 229 individuals treated, 141 had at least one follow-up exam with the mean follow-up interval of 14.6 months +/- 0.9. Ninety -nine patients (70.2%) developed recurrent lesions following the initial treatment. The median interval from treatment to recurrence was four months (range 1-35 months). Those who developed recurrent lesions had a median of two recurrences (range 1-7) during the follow-up period. This frequency of recurrence was similar regardless of HIV status and gender. Conclusions: Anal dysplasia associated with HPV is frequent in men and women regardless of HIV status. Treatment is associated with high recurrence rates. Appropriate surveillance regimens need to be established for women and men.

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A Phase II Clinical Trial of Yttrium-90 Microspheres Selective Internal Radiation Treatment with Concomitant Chemotherapy as a Front-Line Treatment in Patients with Colorectal Cancer Liver Metastases: Evaluation of Objective Tumor Response by Quantitative FDG-PET/CT Imaging S.A. Gulec,* R. Hostetter, K. Pennington, D. Bruetman, T. Fishbach, D. Schwartzentruber. *Center for Cancer Care, Goshen, IN.*

Yttrium-90 (Y-90) microsphere therapy via hepatic arterial administration allows delivery of higher radiation doses to the tumor compartment with relative preservation of liver parenchyma. This study was designed to evaluate the objective tumor responses to concomitant administration of Y-90 microspheres with chemotherapy (Chemo-SIRT)as a front-line therapy in patients with colorectal cancer liver metastases (CRCLM). Methods: Patients with disease limited predominantly to the liver were eligible for the study. The patients underwent a liver-protocol FDG-PET/CT, a visceral angiogram and a 99mTc-MAA scan for disease evaluation and treatment planning. Y-90 resin microspheres (Sirtex Medical, Wilmington, MA) were administered on day 2 of the first chemotherapy (fol-fox or fol-firi)course either lobar or whole-liver fashion. Tumor functional volumes (Vf) were measured on FDG-PET/CT images prior to, and at 4, 8, and 12 weeks after therapy. The relative effectiveness of combined therapy and chemo-only treatment was evaluated comparing functional tumor volume changes in respective lobes in patients who received lobar treatment. Results: 12 pts received single lobe, 3 pts received whole liver treatment. All patients demonstrated tumor Vf decrease in the Chemo-SIRT treated lobe. Mean decreases in Vf in liver field receiving chemo-SIRT and chemo-only were 86.6% and 56.9% respectively($p<0.01$). Tumor Vf decrease was >90% in the target lobe in 8/15 pts. 2 pts had tumor progression in the lobe receiving chemo-only whereas the combined treatment produced sinificant metabolic response. A positive correlation between Vf and pathologic response was observed in patients who underwent resection. Conclusion: Chemo-SIRT as front-line therapy demonstrated significantly improved objective tumor responses as determined by decrease in functional tumor volume. Long term follow-up of these pts is needed to confirm that this response is of clinical significance in terms of recurrence and survival.

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Intersphincteric resection for very low rectal adenocarcinoma: univariate and multivariate analyses of risk factors for recurrence

T. Akasu,* M. Takawa, S. Yamamoto, S. Fujita, Y. Moriya. *Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan.*

INTRODUCTION: Although intersphincteric resection (ISR) reduced the rate of permanent colostomy for patients with very low rectal adenocarcinoma, risk factors for local and distant recurrences are still unclear. Understanding of risk factors for such recurrences may help planning strategy for adjuvant therapy. The aim of this study was to analyze the risk factors for local and distant recurrences following ISR for very low rectal cancer. METHODS: One hundred and twenty consecutive patients with T1–T3 rectal cancers located 1–5 (median 3) cm from the anal verge underwent ISR. Univariate and multivariate analyses of prospectively recorded 26 clinicopathologic parameters from these patients were performed. RESULTS: There were 25 pT1, 46 pT2, 49 pT3, 72pN0, 30pN1, 18pN2 tumors. Pathological stage included stage I in 50 patients, stage II in 21, stage III in 46, and stage IV in 3. Median follow-up time was 3.4 years. The 3-year rates of local and distant recurrences were 6.2 and 13%, respectively. Univariate analysis of the risk factors for local recurrence revealed pT stage, dedifferentiated cells around the tumor, surgical margin, and serum CA 19-9 level to be significant ($P < 0.05$). Multivariate analysis of them showed only surgical margin to be independently significant ($P = 0.002$). Univariate analysis of the risk factors for distant recurrence revealed distance from the anal verge, combined resection, histologic grade, tumor annularity, lymphovascular invasion, neural invasion, pN stage, lateral pelvic lymph node metastasis, adjuvant chemotherapy to be significant ($P < 0.05$). Multivariate analysis of them showed lateral pelvic lymph node metastasis ($P < 0.0001$), pTN ($P = 0.005$), lymphovascular invasion ($P = 0.008$), and distance from the anal verge ($P = 0.020$) to be independently significant ($P = 0.002$). CONCLUSIONS: Profiles of the risk factors for local and distant recurrences were different. The risk factor of local recurrence was surgical margin. Those for distant recurrence were tumor location, lymph node status, and lymphovascular invasion.

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Microscopic Margins and Patterns of Treatment Failure in Resected Pancreas Adenocarcinoma

J.L. Gnerlich,* J. Weir, M. Tan, S.M. Strasberg, W.G. Hawkins, D.C. Linehan. *Department of Surgery, Section of HPB-GI, Washington University School of Medicine, Saint Louis, MO.*

Introduction: Patterns of treatment failure after pancreaticoduodenectomy (PD) with curative intent are inconsistently described in the literature. Local control has gained importance, especially due to controversies surrounding the utility of adjuvant radiation therapy. We report microscopic margin status and its correlation with survival and local control in a large cohort of patients from a high volume pancreas cancer center. Methods: We reviewed patients who underwent standard or pylorus-sparing PD between January 2004 and April 2007. Pancreas adenocarcinoma was confirmed by surgical pathology. A uniform procedure for margin analysis was used which included four color specimen inking (neck, portal vein groove, uncinate, and posterior pancreatic margin) by the surgeon and the pathologist in the operating room. Results: 292 patients underwent PD of which 122 had a diagnosis of pancreatic adenocarcinoma. 22 patients were lost to follow-up. 30 day operative mortality was 2%. Of the analyzable cohort of 100 patients, 27 had one or more positive microscopic margins on surgical pathology (uncinate 16%, portal vein groove 8%, pancreatic neck 6%, and posterior margin 4 %). First site of failure included LR in 5 patients, LR + DR in 23 patients and DR only in 32 patients. Of 28 patients with local failure, 16(57%) had negative microscopic margins. In Chi-square analysis, the presence of any positive microscopic margin correlated with both LR ($p=0.02$) and with overall survival ($p=0.04$). In subset analysis of the four margin sites, only positive posterior pancreatic margin correlated with LR ($p=0.03$). Conclusion: When systematically assessed, the incidence of positive microscopic margins is high, even in high volume centers. Despite a correlation between microscopic margins and LR, the incidence of LR in the absence of DR is rare. The majority of patients with local failure had negative microscopic margins, suggesting that margin status may not be a useful criterion in determining the need for adjuvant radiation.

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Epidermal Growth Factor Receptor (*EGFR*) Intron 1 Polymorphism and Overall Survival in Patients with Pancreatic Adenocarcinoma

J.S. Liles,[1]* A. Frolov,[1] C.D. Tzeng,[1] A. Kossenkov,[2] N.C. Jhala,[1] M.J. Heslin,[1] J.P. Arnoletti.[1] *1. University of Alabama at Birmingham, Birmingham, AL; 2. Wistar Institute, Philadelphia, PA.*

Background: EGFR is overexpressed in a majority of pancreatic adenocarcinoma. *EGFR* intron 1 has a highly polymorphic CA dinucleotide region, ranging from 14 to 24 repeats, which affects transcription efficiency of this receptor. In several epithelial cancers, shorter *EGFR* intron 1 CA repeat length is associated with increased EGFR expression, more aggressive tumors, and worse patient survival. We analyzed *EGFR* intron 1 polymorphism as a prognostic marker of clinical outcome in a large cohort of pancreatic adenocarcinoma patients. Methods: DNA was extracted from surgical specimens in 52 patients with resectable pancreatic adenocarcinoma and from endoscopic ultrasound-fine needle aspiration specimens in 84 patients with unresectable tumors. Allele-specific *EGFR* CA repeat lengths were analyzed by direct sequencing and compared with tumor characteristics, patient demographics, and overall survival in months (mo). Results: Analysis of the entire cohort of pancreatic cancer patients (n=136) revealed no correlation between sum of CA repeats in both alleles (sum) and tumor stage or patient demographics. There was no significant difference in median survival based on allele length (sum<36, 8.1 mo vs. sum≥36, 10.3 mo). As expected, age <70 (11.8 vs. 5.5 mo; log rank, $p=0.002$), stage I/II (13.6 vs. 6.6 mo; $p<0.001$), and surgical resection (20.8 vs. 6.8 mo; $p<0.001$) were associated with improved overall survival. Subset analysis revealed that among the pancreatic cancer patients who underwent surgical resection with curative intent, shorter *EGFR* intron 1 length (sum<36) was found to be significantly associated with decreased overall survival (13.8 vs. 20.7 mo; $p=0.04$). The prognostic influence of *EGFR* intron 1 was not affected by microscopic margin status or administration of adjuvant therapy. Conclusions: Shorter *EGFR* intron 1 polymorphism is associated with decreased overall survival in resectable pancreatic cancer patients. *EGFR* intron 1 status may be incorporated as a prognostic marker of clinical outcome among patients with resectable pancreatic cancer.

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Factors influencing patterns of recurrence and survival following definitive chemo-radiotherapy and salvage therapy for squamous cell carcinoma of the anus

J.F. Flaherty,* N. Joseph, E. Sigurdson, B. Egleston, K. Brown. *Fox Chase Cancer Center, Philadelphia, PA.*

Introduction: Definitive chemoradiation is the standard of care for patients with squamous cell carcinoma of the anal canal and is curative in the majority of cases. The purpose of this study was to identify the clinical and demographic factors that might be predictors of recurrence and survival in this patient population Methods: We used Kaplan-Meier survival estimators and Cox proportional hazards models to investigate overall, disease free survival, and post-recurrence survival. Results: Forty-eight individuals were included in the dataset. The estimated 3-year overall survival rate was 76.4% (95% CI 60.4%-86.6%), while the estimated disease free survival rate was 62.5% (95% CI 45.9%-75.4%). Recurrences were local 61% of the time and distant 38% of the time. In Cox models, having stage 3 or 4 disease was associated with worse outcomes (hazard ratio [HR]=12.4, $p=0.001$ in the overall survival model, HR=8.5, $p<0.001$ in the disease free survival model). The probability of recurrence at 3 years was estimated to be 26.7% (95% CI 12.7%-40.7%). In multivariate analyses, documented HPV infection was associated with being less likely to have a recurrence($p<0.001$), while having stage 3 or 4 disease ($p=0.012$), and being African American ($p=0.003$) were associated with being more likely to have a recurrence. Conclusion: Our study confirms the stage-related effect on recurrence seen by others but suggests a "protective" effect with respect to recurrence and survival where a history of human papilloma virus is documented. HPV portends a better prognosis in squamous cell cancers of the head and neck as well. The reason for this is unclear and warrants further investigation. We also note that being African American functions as an independent variable in multivariate analysis predicting a greater likelihood for recurrence and death. This finding is also seen in other cancers. Socioeconomic factors including access to healthcare and education may play a role but the biologic explanation for race-related increase recurrence rates in similar stage patients remains elusive and demands further study.

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The Effect of Abrogating the TGFβ Pathway on Metastases in an Orthotopic Model of Colon Cancer I. Dominguez,[2]* J. Wang,[3] E. Sharratt,[1] M. Brattain,[3] A. Rajput.[1] *1. Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; 2. The University at Buffalo—SUNY, Buffalo, NY; 3. University of Nebraska, Omaha, NE.*

Introduction: Colorectal cancer is a leading cause of cancer related mortality in the USA. Transforming Growth Factor Beta (TGFβ) is inhibitory to colonic epithelium and the TGFβ Type II Receptor (TGFβ RII) is an established tumor suppressor gene. There are few in vivo models which allow for the study of metastasis. The purpose of this study was to determine the effect of abrogating the TGFβ pathway in FETα, a human colon cancer cell line in an orthotopic model of colon cancer. Methods: FETα colon cancer cells were stably transfected with a Dominant Negative RII construct to create a cell line, FETαDNRII which is no longer inhibited by TGFβ. Both cell lines were also stably transfected with green fluorescent protein (GFP) to allow for serial in vivo imaging. 7 x 106 cells of each line were subcutaneously injected into BALB/c nude mice to generate xenografts. Once established, these xenografts were explanted, minced into 1 mm3 pieces and then 2 pieces were subserosally implanted onto the colons of other BALB/c nude mice. (n=24 FETα, n=30 FETαDNRII). GFP imaging was performed weekly to follow tumor growth and progression for 7-8 weeks at which time animals were necropsied. Tissues were formalin fixed and paraffin embedded for H&E examination. Results: All animals in both groups demonstrated primary tumor growth on GFP imaging and tissue invasion at the sites of implantation on the colon on H&E staining. In the FETα implanted animals, 0/24 demonstrated any liver or lung metastases on H&E staining of tissues serially sectioned. In the FETαDNRII implanted animals 5/30 (17%) demonstrated liver metastases and 26/30 (87%) demonstrated lung metastases upon histologic examination. Conclusions: The FETα human colon cancer cell line is tumorigenic, but not metastatic in an orthotopic model of colon cancer. By introducing a DNRII gene into FETα and therefore abrogating the TGFβ signaling pathway, the FETαDNRII cell line is not only tumorigenic, but metastatic in this in vivo model system. Thus, reconstitution of the TGFβ pathway in cancers where the pathway is dysregulated may allow for a novel molecular therapeutic intervention.

Results of Orthotopic Implantation

Cell Line	Primary Invasion	Liver Metastases	Lung Metastases
FETα	24/24 (100%)	0/24 (0%)	0/24 (0%)
FETαDNRII	30/30 (100%)	5/30 (17%)	26/30 (87%)

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Peritonectomy and Intraperitoneal Chemotherapy with and without Hyperthermia for Colorectal Cancer. Prospective Study A. Cravioto,* A. Cu-Cañetas, P. Luna-Perez, S. Rodriguez-Ramirez, H. Martinez-Gomez, L. Ramirez, E. Rodriguez-Antezana. *Hospital de Oncologia, Centro Medico Nacional Siglo XXI, Mexico City, Mexico.*

INTRODUCTION Despite multiple phase II and III studies have demonstrated that long term survival is possible with hyperthermic intraperitoneal chemotherapy, there are no clinical controlled trials that compares patients with cytoreductive surgery and intraperitoneal chemotherapy with and without hyperthermia.OBJECTIVE To determine if hyperthermia is a prognostic factor of survival in patients with carcinomatosis of colorectal origin. PATIENTS AND METHODS From January 2001 to January 2007, 34 patients where included in the study. Patients were divided into two groups, 13 patients that received Hyperthermic intraperitoneal chemotherapy and 21 patients that received normothermia intraperitoneal chemotherapy. RESULTS The study group included 21 female patients and 13 male with a mean age of 54.9 (range 17-81).Adenocarcinoma in 22 patients and Pseudomyxoma in 12 patients Surgery was considered CC0 in 41.2 percent of patients, CC1 in 11.8 percent, CC2 in 23.5 and CC3 in 23.5 percent. The 5-year disease free survival was of 26%, with a mean value of 26.35 months. Two-year disease free survival for hyperthermia group was of 27%. Two-year disease free survival for normothermia group was of 54%. No statistical difference was found (p=0.39) No differences were found when analyzing adenocarcinoma and pseudomyxoma patients treated with hyperthermia and normothermia Five year global survival of all group was of 30%. No difference in 5-year survival was found between patients that received hyperthermia and patients that received normothermia (p=0.54) 5-year survival was statistically significative for the CC0 patients. Patients considered with CC0 surgery had a 5 year survival of 46 percent, compared with 8 percent of CC1, CC2 and CC3 group (p<0.05) There was no difference between CC0 patients with hyperthermia and CC0 patients with normothermia. (p=0.47). In multivariate analysis, CC0 surgery was the most significative factor (p<0.05) CONCLUSIONS Complete cytoreduction is the most important factor for survival, independently of the temperature used during intraperitoneal chemotherapy.

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A Tumor-Positive Sentinel Node Biopsy of the Groin in Melanoma Patients: Superficial or Superficial and Deep Lymph Node Dissection? I.M. Van der Ploeg,* O.E. Nieweg, R.A. Valdés Olmos, B.B. Kroon. *The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.*

Introduction: The extent of a groin lymph node dissection in melanoma patients with a sentinel node metastasis is controversial. Most surgeons perform a superficial (femoro-inguinal) dissection, but some opt for a more radical approach combining a superficial and deep (iliacal, obturator) dissection. The purpose of this study was to shed light on this controversial issue. Methods: Lymphoscintigraphy was performed before the sentinel node biopsy using 99mTc-nanocolloid, which has a fairly small particle size. Between June 1996 and April 2007, 42 patients underwent completion groin dissection after a tumor-positive femoro-inguinal sentinel node biopsy. Results: The scans that had been used for the sentinel node biopsy were reviewed. Second-tier nodes were always visualized. Higher-echelon nodes were neglected. Eighteen of the 42 patients had superficial second-echelon nodes and they underwent a superficial lymph node dissection. The other 24 patients had deep second-echelon nodes and they underwent a combined superficial and deep dissection. This approach was based on the assumption that second-echelon nodes are most at risk for additional metastases. The median follow-up time was 61 months. For the 42 patients combined, the five-year overall survival is 77% and the disease-free survival 56%. One of the 18 patients who underwent a superficial groin dissection developed a deep (obturator) lymph node recurrence after 12 months. Revision of the lymphoscintigram showed that the images had been interpreted incorrectly and that the second-echelon node was located in the obturator area after all. This patient is alive and without signs of disease eight years later. A combined superficial and deep dissection revealed additional involved nodes in the deep lymph node compartment in two of the 24 patients. One of them developed local and distant metastases and died 26 months after the initial dissection, the other patient is alive without evidence of disease after 14 months. Conclusion: This limited series suggests that the strategy to determine the extent of the groin dissection based on the location of the second-tier nodes is valid.

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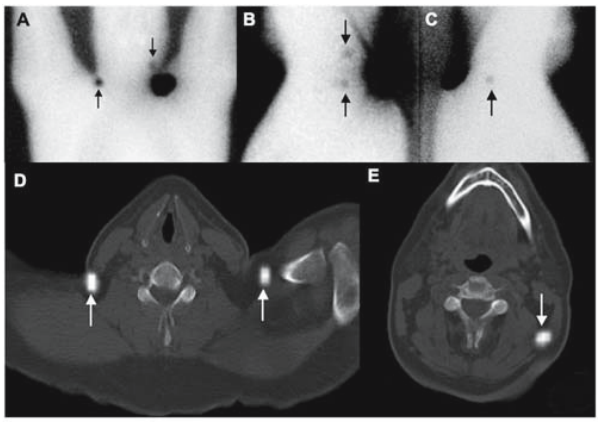
The Additional Value of SPECT/CT in Lymphatic Mapping in Melanoma Patients I.M. Van der Ploeg,* R.A. Valdés Olmos, O.E. Nieweg, B.B. Kroon. *The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.*

Introduction: The recently introduced single photon emission computed tomography camera with integrated CT (SPECT/CT) fuses tomographic lymphoscintigrams with the anatomical data of CT. The purpose of this study was to explore the additional value of SPECT/CT in lymphatic mapping in melanoma patients with unusual drainage or a problematic conventional scan. Methods: Twenty patients were studied, 7 women and 13 men. Eleven had a melanoma on the trunk, one on the leg and 8 in the head and neck region. Results: The reasons for performing additional SPECT/CT were conventional lymphoscintigrams with an unusual lymphatic drainage pattern (7 patients), conventional images that were difficult to interpret, e.g. nearby injection site, (12 patients) or non-visualization (1 patient). SPECT/CT did not require an extra injection of

the radiopharmaceutical and was done immediately following conventional imaging. Conventional lymphoscintigrams visualized 58 sentinel nodes in 20 patients. SPECT/CT showed these same nodes plus 6 additional sentinel nodes in 4 (20%) of the patients. Two of these 6 additional nodes were detected in the patient with non-visualization. Another two of the 6 additional nodes could not be harvested due to the small amount of radioactivity and lack of a blue lymph vessel. Eventually, 4 additionally visualized sentinel nodes were harvested in 3 patients, of which one was tumor-positive and prompted a regional node dissection. In all patients, SPECT/CT showed the precise anatomical location of sentinel nodes in lymph node basins (figure) and in unusual locations. SPECT/CT facilitated identification of sentinel nodes adjacent to the injection site of the radiopharmaceutical. Invariably, surgeons stated that SPECT/CT improved their notion of the location of the sentinel nodes and helped them to better plan the operation. Conclusion: SPECT/CT led to upstaging and a change in management in one of the 20 patients. SPECT/CT detects additional sentinel nodes and shows the exact anatomical location of sentinel nodes in melanoma patients with inconclusive conventional lymphoscintigrams or non-visualization. SPECT/CT facilitates surgical exploration in difficult cases.



A man with a melanoma on the back medially from the left scapula. Conventional anterior imaging (A) and a left (B) and right (C) lateral view visualize a sentinel node on either side of the neck (ascending arrows) and suggest these to be in the dorsal neck. A third sentinel node is depicted cranial from the primary tumor site (descending arrows). SPECT/CT (D) shows the first two nodes (ascending arrows) to be in fact located in the supraclavicular region on each side. This finding prompted the surgeon to place the patient on the operating table in the supine position rather than the prone position. The exact anatomical location of the third sentinel node (descending arrow) is shown on the right SPECT/CT image (E).

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Systemic Thermal Therapy Alters the Non-permissive Tumor Microenvironment During Adoptive Immunotherapy J. Skitzki,* Q. Chen, D. Fisher, J. Muhitch, C. Villegas, J. Kane, S. Evans. *Surgery, Roswell Park Cancer Institute, Buffalo, NY.*

Background: Tumor microenvironments are hypothesized to become refractory to lymphocyte entry, limiting the effectiveness of adoptive immunotherapy. As systemic thermal therapy (STT) can improve lymphocyte entry into secondary lymphoid organs by increasing adhesive properties of lymphocytes and vascular endothelium, STT may also be able to alter tumor microenvironment permissiveness to activated lymphocytes. Methods: Murine melanoma B16/F10 cells transfected with the neoantigen ovalbumin (B16-ova) and ovalbumin specific CD8+ T lymphocytes from transgenic mice (OT-1) were used for adoptive transfer experiments. Normothermic (NT) mice with established subcutaneous B16-ova tumors (3, 7, or 14 days) were injected with activated/expanded OT-1 lymphocytes and immunohistochemistry (IHC) was used to assess tumor infiltrating OT-1 cells. STT (39.5±0.5°C for 6h) was then performed prior to adoptive cell transfer in the 7 day model. Tumor vasculature, adoptively transferred cells, and tumor growth were evaluated for STT versus NT (5 mice/group). Results: The extent of tumor infiltrating adoptively transferred OT-1 lymphocytes was inversely proportional to tumor age and size (and was negligible in 14 day established tumors). Importantly, these findings were not due to differences in availability of OT-1 cells between groups. Following STT, tumor vasculature intercellular adhesion molecule 1 (ICAM-1) expression was markedly increased versus NT. In contrast to endothelium, B16-ova cells lacked inducible ICAM-1 expression both in vivo and in vitro. There was a ~6 fold increase in OT-1 cell homing following STT versus NT at both 1 hour and 24 hours ($p<0.001$). STT prior to adoptive transfer produced a statistically significant reduction in tumor growth (~50% within 6 days of treatment) versus NT. STT alone (without adoptive transfer) did not affect tumor growth or overall survival. Conclusions: Established tumors treated with SST prior to adoptive lymphocyte transfer exhibit increased ICAM-1 expression, lymphocyte infiltration, and decreased growth kinetics as compared to NT. SST may warrant further study in clinical cancer adoptive immunotherapy.

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S100B Levels Are More Accurate than LDH Levels at Predicting Survival in Melanoma Patients Y.S. Chun,* Y. Wang, D.Y. Wang, D.M. McClain, A. Lucci, P.F. Mansfield, J.N. Cormier, M.I. Ross, J.E. Gershenwald, J.E. Lee. *The Univ. of Texas M. D. Anderson Cancer Center, Houston, TX.*

Introduction: The serum level of S100B has been proposed as a melanoma prognostic marker, and LDH has been incorporated into the current AJCC staging system for patients with stage IV melanoma; however, limited data exist regarding their relative utility. We therefore investigated associations between these blood markers and survival in a group of prospectively followed melanoma patients. Methods: Patients with all stages of disease underwent blood draw for simultaneous LDH and S100B determination. Clinicians were blinded to S100B but not LDH results. Clinical data was obtained from a comprehensive melanoma patient database; all patients underwent standardized evaluation and prospective follow-up. Stage of disease and length of follow-up were determined from the date of blood draw. An S100B level of >2.0 mcg/L and an LDH level of >618 U/L were considered elevated. Results: Paired S100B and LDH levels were obtained from 566 patients (384 stages I-II, 129 stage III, 53 stage IV). S100B was elevated in 87 patients (15%) and LDH was elevated in 42 (7%); 60 patients (69%) with an elevated S100B had a normal LDH. There were strong correlations between stage and both S100B ($P<0.0001$) and LDH ($P<0.0001$): elevations of S100B and LDH were seen in 7% and 3% of stages I-II, 17% and 5% stage III, and 72% and 43% of stage IV patients respectively. After a median follow-up of 11 months, 38 patients (6.7%) had progressed and 30 (5.3%) had died. S100B and LDH levels, as well as stage, were associated with overall survival (OS) on univariate analysis, while S100B and stage, but not LDH, were independent predictors of OS on multivariate analysis (Table). Subgroup analysis confirmed that S100B was a predictor of OS in both stage III ($P<0.0001$) as well as stage IV ($P=0.05$) patients. Conclusions: An elevated S100B level is a predictor of poor survival in melanoma patients and appears to provide better independent prognostic information compared to an elevated LDH. While additional follow-up will be necessary to determine the utility of S100B in early-stage melanoma, S100B may assist in selecting high-risk stage III melanoma patients for more intensive follow-up or for adjuvant therapy trials.

Association of stage, S100B and LDH with OS in 566 melanoma patients

Prognostic factor	Univariate P	Multivariate P	HR (95% CI)
Age	0.149	-	-
Gender	0.463	-	-
Stage at blood draw	< 0.0001	< 0.0001	
Elevated S100B	< 0.0001	0.046	2.26 (1.02-5.04)
Elevated LDH	< 0.0001	0.278	-

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Low-dose IL-2 upregulates expression of chemokine receptor CXCR3 on antigen-experienced CD8+ T cells in patients with metastatic melanoma L.T. Dengel,[1]* E.C. Glassberg,[3] M.D. Burdick,[2] R.M. Strieter,[2] C.L. Slingluff,[1] D.M. Mullins.[3] *1. University of Virginia Health System Department of Surgery, Charlottesville, VA; 2. University of Virginia Health System Department of Medicine, Charlottesville, VA; 3. University of Virginia Health System Department of Microbiology, Charlottesville, VA.*

INTRODUCTION: Despite the presence of tumor Ag-specific T cells in the periphery of vaccinated patients, melanoma evades immune-mediated destruction. Optimizing T cell trafficking is essential to immunotherapy and may be facilitated by enhanced chemokine receptor interactions. Interleukin-2 (IL-2) at high-doses upregulates the chemokine receptor CXCR3 on T cells, but effects of a less toxic regimen on expression of CXCR3 and its ligands are not known. METHODS: Peripheral blood was evaluated from 9 patients with metastatic melanoma who were treated on a previous protocol with a vaccine and 6 weeks of daily low-dose IL-2 (3Mu/m2/d sc). CXCR3 expression on antigen-experienced (CD45RO+) CD8+ T cells was determined by flow cytometry. Also, levels of CXCR3 ligands in serum and metastatic melanoma were measured by ELISA and immunohistochemistry, respectively. RESULTS: CXCR3 was expressed on an average of 2.9% of antigen-experienced CD8+ T cells, prior to induction of IL-2, increasing to 14.1% peak expression ($p=0.001$) a median 5.1 fold increase (2.4-15.1). Increased CXCR3 expression was evident as early as 1 week after initiation of low dose IL-2. Eight patients with metastatic melanoma treated with the same vaccine regimen, but without IL-2, were evaluated as controls and had no change in CXCR3 expression ($p=0.813$). In the 9 patients who received low-dose IL-2, there was no change in serum levels of CXCR3 ligands after initiation of the IL-2. Interestingly, CXCL9 was expressed by vascular endothelium in human metastatic melanoma. CONCLUSIONS: These findings suggest a possible role for low-dose IL-2 in upregulating CXCR3 expression on CD8+ T cells after melanoma vaccines in order to target the immune cells to tumor. The serum gradient for CXCL3 ligands does not appear to be disrupted during low-dose IL-2; however, it is known that type I IFN may increase expression of these ligands. These data support clinical investigation of low dose IL-2 to upregulate CXCR3 expression by vaccine-stimulated T cells and use of intralesional IFN to upregulate CXCR3 ligands in metastatic melanomas, to improve T cell trafficking to tumor.

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Pelvic Lymph Node Metastases in Patients with Lower Extremity Melanoma: New Techniques to Identify Patients at Risk S. Carpenter,* B. Pockaj, R. Gray, M. Roarke, W. Casey. *Mayo Clinic School of Graduate Medical Education, Phoenix, AZ.*

BACKGROUND: The incidence of pelvic node metastases and indications for pelvic lymphadenectomy (LA) for lower extremity melanoma (LEM) are poorly defined. METHODS: Retrospective review of all patients with LEM who underwent sentinel lymph node (SLN) biopsy 1997-2007. Patients underwent preoperative planar lymphoscintigraphy (LS). SPECT/CT lymphoscintigraphy (SCLS) was additionally performed beginning October 2006. All patients with pelvic lymph node (PLN) drainage on preoperative LS and positive inguinal SLN were treated with laparoscopic pelvic LA beginning in August 2004. RESULTS: 107 patients with LEM underwent LS and SLN biopsy. Mean age was 59 (15-87), 65% were female. Mean Breslow thickness was 2.3 mm (0.3-8.0mm). PLN primary or secondary drainage was seen on LS in 37 patients (35%) including 11 of 13 patients (92%) undergoing SCLS. 19 patients (18%) had inguinal SLN metastases. 15 of those (79%) underwent completion inguinal LA alone and 3 (16%) underwent combined completion inguinal LA and laparoscopic pelvic LA. 6 patients (33%) had additional lymph node metastases including one with a PLN metastasis (1% of all patients, 33% of those undergoing pelvic LA). 5 of the remaining 104 patients (5%) experienced PLN recurrence. 3 of those had PLN drainage on LS. The overall rate of PLN metastases was 6%. 2 patients (40%) with PLN recurrences had previous inguinal SLN metastases, but 3 recurred with previously negative inguinal SLNs. 2 of the 5 patients with PLN recurrence had concurrently diagnosed systemic disease and suffered melanoma-related deaths. The other 3 patients underwent salvage pelvic LA, and 2 of these were disease free at 72 and 16 months of follow-up. The third died of other causes. CONCLUSION: The rate of PLN metastases among patients with LEM is 6%. SCLS identifies PLN drainage more often than LS. Laparoscopic pelvic LA can facilitate early diagnosis of PLN metastases for patients with inguinal SLN metastases and pelvic drainage on LS, but PLN recurrences can occur with negative inguinal SLNs and no evidence of pelvic drainage on LS. Patients with isolated PLN recurrences can be successfully salvaged with surgery.

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Molecular Profiling of Primary Melanoma: A Look at the Biology R. Essner,* J.H. Lee, H. Itakura, Y. Huynh. *Molecular Therapeutics, John Wayne Cancer Institute, Santa Monica, CA.*

Introduction: While most primary melanoma can be cured by surgery alone, 20-30% of tumors will metastasize to regional lymph nodes or distant sites. We previously preformed cDNA microarray analyses using a chip focused on metastasis related genes, of intact primary melanoma; demonstrating upregulation of vascular endothelial growth factor (VEGF) and Lim Kinase (LIMK) from primaries that ultimately manifest metastases. We undertook this study to validate the significance of these 2 genes by quantitative PCR. Methods: Primary melanoma specimens were obtained from 39 patients who underwent wide excision alone or with sentinel lymph node dissection. Tumor specimens and normal skin matches were evaluated by quantitative real-time reverse transcription PCR (qRT-PCR). The protocol was approved by the Institutional IRB. Tangential peripheral sections were collected from freshly collected tissue and placed in RNA later (Qiagen). Sample RNA was processed by qRT-PCR using primer and probe sequences purchased from Applied Biosystems. PCR amplification was standardized against diluted plasmid cDNA controls allowing us to calculate threshold cycle (Ct) and mRNA copy number (ABI Prism 7000 SDS software). Results: Fresh RNA was obtained from primary cutaneous melanoma and normal adjacent skin specimens. mRNA copy number was calculated for tumor specimen and normalized to adjacent skin. Median mRNA levels were evaluated and compared by Wilcox test. Increasing expression of VEGF correlated with primary tumor size ($p=0.0078$). LIMK expression was related to head and neck primaries ($p=0.0078$), increasing tumor thickness ($p=0.029$), size ($p=0.0043$) and Clark level ($p=0.015$). Neither VEGF nor LIMK gene expression correlated with age, gender, or presence of ulceration at the primary site. Conclusions: The molecular mechanisms that regulate expression of melanoma metastases are unknown. We have identified VEGF and LIMK as two potential candidates; both genes are upregulated with advancing local tumor stage.

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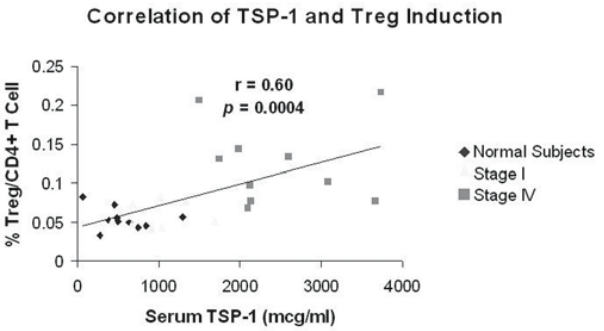
Proportion of Circulating Regulatory T Cells Correlates with Serum Thrombospondin-1 in Melanoma Patients J. Baumgarter,* R. Gonzalez, K. Lewis, W. Robinson, A. Banerjee, M. McCarter. *Surgery, University of Colorado Health Sciences Center, Denver, CO.*

Introduction: Melanoma is associated with the presence of an increased population of regulatory T cells (Tregs). Thrombospondin-1 (TSP-1) is a matricellular protein involved in tissue remodeling and inflammation and has recently been described to generate Tregs. We hypothesized that melanoma induces Tregs through the secretion of TSP-1. Methods: Normal, stage I and stage IV melanoma patient serum samples and peripheral blood mononuclear cells (PBMCs) were collected and the quantity of serum TSP-1 was determined by ELISA and the percentage of Tregs in all CD4+ T cells was determined by flow cytometry. For in vitro experiments, control media, benign fibroblast-conditioned media (FCM) and several cell lines of melanoma-conditioned media (MCM) were probed for TSP-1 by Western blot. Normal human PBMCs were also exposed to these conditioned media and analyzed by flow cytometry for Treg induction using CD4 and FOXP3 antibodies, and this induction was correlated with the amount of TSP-1 on Western blot by the Pearson correlation coefficient. Results: We have previously found stage IV melanoma patients to

have higher proportions of circulating immunosuppressive Tregs than normal subjects or stage I patients (12% v. 6% for normal and stage I patients, respectively, $p < 0.01$). In this study, stage IV melanoma patients also had higher plasma levels of TSP-1 than normal or stage I melanoma patients (2471 ± 247 v. 569 ± 106 and 914 ± 120 μg/ml, respectively, $p < 0.05$), and this directly correlated with the percentage of circulating regulatory T cells in all subjects (figure). As described in a previous in vitro study, exposure to some but not all MCM resulted in induction of Tregs in normal PBMCs. When this induction was compared to the amount of TSP-1 in each MCM, the amount of TSP-1 on Western blot was directly proportional to the ability of MCM to induce Tregs ($r = 0.72$, $p = 0.006$). Conclusion: Melanoma induces regulatory T cells through secretion of thrombospondin-1, thereby providing a potential mechanism by which melanoma evades the immune response.



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SPECT/CT Enhances Pre-Operative Lymphatic Mapping

B.U. Laxa,[1]* B.A. Pockaj,[1] M.C. Roarke,[2] R.J. Gray.[1] *1. Department of Surgery, Mayo Clinic Arizona, Phoenix, AZ; 2. Department of Radiology, Mayo Clinic Arizona, Phoenix, AZ.*

Introduction: Standard lymphoscintigraphy (LS) identifies the lymphatic drainage in patients with cutaneous malignancies who undergo sentinel lymph node (SLN) biopsy. SPECT/CT lymphoscintigraphy provides superior anatomic detail in relation to the SLN location but its use for pre-operative lymphatic mapping has not been well defined. Methods: Retrospective review of all patients who underwent LS and SPECT/CT for cutaneous malignancies. To determine if there was additional information provided by SPECT/CT, a surgeon and radiologist performed a blinded review of the LS followed by SPECT/CT. Results: 62 patients underwent both imaging modalities. Primary tumor location was upper extremity (22%), lower extremity (26%), trunk (22%), and head and neck (31%). Preoperative imaging demonstrated drainage to 80 lymph node (LN) basins: groin (26%), axilla (33%), neck (33%), and in-transit (9%). Multiple LN basins were detected in 26% of patients. At surgery, the SLN was identified in 98% of cases with an average of 2.2 SLNs removed per basin. 7 patients (11%) had a positive SLN. Surgical and radiologic review of the pre-operative lymphatic mapping revealed that SPECT/CT clarified or changed the radiographic interpretation and/or surgical approach in 64% of cases. SPECT/CT was helpful for patients with drainage to the neck, groin, and in-transit SLNs. The anatomic detail provided by SPECT/CT was especially beneficial in patients with lymphatic drainage to the neck. Drainage to both groin and pelvic SLNs was better delineated by SPECT/CT thus identifying patients at risk for pelvic LN metastases. 2 patients with a positive groin SLN and a SPECT/CT demonstrating pelvic lymphatic drainage were found to have positive pelvic LN after laparoscopic pelvic LN dissection. There was no advantage of SPECT/CT in patients whose lymphatic mapping was limited to the axilla or upper extremity in-transit SLNs. Conclusions: SPECT/CT facilitates SLN biopsy by providing better anatomic detail in relationship to the SLN. The benefit of SPECT/CT was greatest in patients who mapped to the groin, neck, and trunk in-transit LNs whereas there was little impact with drainage to the axilla and upper extremity in-transit SLNs.

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Thick Primary Melanomas: A Heterogeneous Tumor Biology?

A. Meguerditchian,* K. Asubonteng, C.J. Young, B. Lema, G. Wilding, J.M. Kane III. *Roswell Park Cancer Institute, Buffalo, NY.*

INTRODUCTION Thick primary melanomas (TM) ≥4mm traditionally have a high risk for nodal/ distant metastatic disease. Optimal surgical management, prognostic significance of sentinel lymph node biopsy (SLNB), and potential benefits of adjuvant interferon (IFN) are not well defined. As a continuum of increasing tumor thickness is placed into a single TM group, differences in biologic behavior/clinical outcome may also be lost. METHODS Retrospective review of 155 TM patients treated at a single institution from 1971-2006. Demographics, tumor features, surgical and adjuvant therapy, and outcome were evaluated. The range of tumor thickness was also analyzed as groups around the median. RESULTS Median age was 66 years and 68% were male. Primary location was 35% trunk, 35% extremity, 30% H&N. Median thickness was 6 mm (range 4 – 50 mm) and 61% were ulcerated. 7% (11) patients had synchronous stage IV disease and 12% (20) had clinical nodal metastases. 24 patients underwent elective lymph node dissection (ELND) and 75% (18) were positive. SLNB was performed in 91 patients and was positive in 44% (40/91). Completion node dissection was performed in 90% (36/40) SLNB positive patients. 17% (24/144) received IFN. Median follow up was 26 months (range 2–148 months). For the entire group, 5 and 10 year disease-free survival (DFS) were 42% and 24% and overall survival (OS) were 44% and 24%. For SLNB positive vs negative, median DFS were 22 vs 111 months and median OS were 41 vs 111 months. When stratified by tumor thickness ≤ vs > 6 mm, 5 and 10 year DFS were 58% and 28% vs 20% and 13% and OS were 62% and 28% vs 20% and 13%, respectively. IFN had no impact on DFS or OS (p=0.98 and 0.81). Tumor thickness > 6 mm and a positive SLNB were significantly associated with a decreased DFS and OS (p< .0001, <.0001 and .006, .006). CONCLUSION SLNB status is highly predictive of outcome in TM with almost 2/3 of SLNB negative patients alive at 5 years. There appear to be two different biologies in TM: tumors 4-6 mm have a sustained risk for recurrence/death over 10 years while "ultra thick" melanomas (> 6mm) have a high risk for early recurrence/death that significantly decreases after 5 years.

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Acute Normovolemic Hemodilution (ANH) in Oncologic Surgery

K.M. Brown,* M.R. Reed, W.G. Kraybill, C.M. Richart. *St. Luke's Cancer Institute, Kansas City, MO.*

Background: Much evidence supports the negative impact of blood transfusions on operative outcomes and survival. ANH has been shown to reduce transfusion requirements, but is not well-described in oncologic surgery. Thus, patients (pts) whose religious tenets preclude blood transfusion may not be offered radical oncologic surgery. Methods: A retrospective review was undertaken of pts undergoing ANH with intra-abdominal tumors. Preoperative and intraoperative factors were reviewed. Postoperative course including morbidity, mortality, length of stay (LOS) and transfusion requirements were abstracted from medical records. Results: From May 2006- July 2007, 8 pts undergoing resection of an intra-abdominal tumor using ANH were identified. Median age was 57 years (range 44-93); 62% were male. Tumors included colon cancer (3), sarcoma (1), GIST (2), hepatocellular (1) and adenocarcinoma of unknown primary (1). Resections included colon in 5, liver in 2 and pancreas in 1. Median initial hematocrit (Hct) for pts receiving preoperative (preop) iron and erythropoietin (5 pts) was 29% (range 25-45%); median Hct immediately preop was 43% (range 31-50%). One Jehovah's Witness (JW) patient underwent emergent Whipple for hemorrhage; the rest were elective. Median blood sequestered was 1200ml (259-1900 ml). Time from starting ANH to incision was a median of 31 minutes (range 0-54 minutes). The median EBL was 1500 ml (260-3500), and patients received a median of 7.8L of crystalloid (range 2.9-20L). The median operating time was 354 minutes (259-730 minutes). Two non-JW pts received allogeneic blood - 1 received 4 units packed red blood cells (PRBCs) intraoperatively and 1 received 3 units PRBCs postoperatively. There were no operative mortalities, and a median LOS of 11 days (range 5-23 days). Four pts (50%) experienced complications: pneumonia, pulmonary embolism, atrial fibrillation, and bowel obstruction. Conclusions: ANH can be used as an adjunct to minimize blood transfusions in pts undergoing major resections for intra-abdominal malignancies with acceptable morbidity and mortality. This technique may be especially useful in JW pts. Additional prospective study is needed to assess survival and recurrence.

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The Impact of Radical Bowel Resection during Primary Surgery for the Recurrence and Survival in Epithelial Ovarian Cancer S. Saha,* S. Sirop, D. Iddings, M. Ghanem, N. Dutt, J. Metz, D. Wiese, T. Singh, M. Arora, D. Eilender. *McLaren Regional Medical Center, Flint, MI.*

Introduction: Ovarian cancer(OvCa) often initially presents in advanced stages(III and IV). The median survival of patients(pts) with stage III or IV OvCa undergoing optimal cytoreduction(OpCR) is 37 months according to a recent meta-analysis by Fader et al of 3245 pts. The role of radical bowel resection(BR) to achieve OpCR remains controversial; hence, a retrospective analysis was done to assess the safety of radical BR and its impact on recurrence and survival in pts with advanced OvCa. **Methods:** A retrospective review of 154 consecutive pts with epithelial OvCa between August 1991 and December 2006 was undertaken. Data was obtained for age, stage of the disease, operative procedure, recurrence and survival. Recurrence and survival were compared to control data from the meta-analysis, using the student t-test for significance. **Results:** Forty-Eight pts(48/154; 31.2%); with a median age of 65 years, underwent radical BR during the primary surgery to achieve OpCR. Thirty eight pts(79.2%) had stage III and 5 (10.4%) had stage IV disease. Pts were followed until death and the median follow up of the surviving pts was 46 months. Of the 48 pts, 32 had large BR, 5 had small BR, 6 had both small and large BR and 5 had partial gastrectomy. Bowel continuity was maintained in 37 pts(77.1%). There was no perioperative mortality, and the most common morbidity was prolonged ileus with no serious complications of fistula or bowel obstruction. Twenty seven pts(56%) received neoadjuvant chemotherapy and 19 (39.6%) underwent adjuvant chemotherapy only; two pts refused further treatment. Overall median survival of stage III and IV patients was 35.5 months with a 2-year survival rate of 54.2%. Recurrence developed in 39% of pts(37% of stage III pts and 60% of stage IV pts) with a median disease-free interval of 26 months. **Conclusion:** Bowel Involvement did not independently effect the overall survival of patients with stage III and IV OvCa if OpCR could be performed and should not prohibit efforts to achieve OpCR. Radical BR is safe to perform and the survival of our patients was similar to the meta-analysis reported survival (35.5 vs 37 months, p=0.67).

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Analysis of demographic factors in carcinoma breast patients over the last 10 years B. Selvan,* D. Abraham, M.J. Paul. *general surgery, christian Medical College, Vellore, Tamilnadu, India.*

Background This study is basically looking at various demographic features as a causative factors for the development of carcinoma breast and this is not been described in asian population Materials and methods We have analyzed in patient and out patient charts of 680 patients who had undergone surgery for carcinoma breast in our department. Results Among 680 the mean age was 44 years,majority of them are distributed equally between 3 rd and 4 th decade .The median BMI was 26[27%] which is in the overweight side. 102[15 %] of them are unmarried and 68[10%] have no children. 360[53%] have equal or more than two children..442[65%] have features of mastalgia at some time before the diagnosis of disease.27[4%] have one of their first degree relative the disease and the overall positive history of breast carcinoma is 7%. 333[49%] have treatment for ANDI at some period of time.44% of them have commercially available either pork or chicken. Early menarche, less than 12 years seen in only 8% .Age at first child was less than 20 yrs in 14%,10 % of them have their first child after 30 years. In 22% of the patients, carcinoma occurs after 20 years since the last child birth. 163[24%] have equal or more than one abortion before the diagnosis of the carcinoma .19 % have history of having hysterectomy and early surgical menopause.42% are in the premenopausal stage,chemo induced menopause was observed in 54% of the patients . Conclusion: The age at which the disease is diagnosed is in the 3rd decade of age . Nulliparous has incidence up to 24%. ANDI definitely seems to have independent risk factor,another independent factors emerging is having history of equal or more than one abortion and early hysterectomy. The familial incidence is around 4%.

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The Alberta WEB SMR: Synoptic Operative Reporting; Outcomes system for the future W.P. Francis,* K. Dabbs, E. Tamano, T. Fields, T. Gomes, W.J. Temple. *Surgical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada.*

Introduction. The concept of synoptic operative reporting has now been proven with the implementation of the Alberta WEB SMR. It allowed us to analyze its utility in providing surgeon generated outcomes related to decision making, resource utilization, adherence to guidelines, as well as operative technique on a real time basis using breast cancer as an example. Methods. A synoptic breast cancer template was created using a modified Delphi process with university, urban and rural contributing surgeons. This was digitized and made available to all surgeons on the WEB via a secured centralized data base. The concept of the operative report was expanded to record the pre-op knowledge of the surgeon on critical issues which would influence the patient's management. Real time short term outcomes of personal data (PD) as well as provincial aggregate data (AD) were provided to each surgeon, with updates within 24 hours of entry. Results. The data references 563 breast cancer procedures entered by 18 surgeons from December 2005 to August 2007. Breast cancer detection by mammography was disappointingly low at 45% compared to patient detection rate at 48% (p=0.3702), considering the presence of a well established free screening program. The overall breast conservative surgery (BCS) rate was dramatically altered from 48% to 80% when analyzed for those patients that were eligible (p<0.0001). In patients receiving mastectomy 80% had an absolute indication. The AD revealed that the method for lymph node staging was in contrast to current guidelines advocating full axillary lymph node dissection (ALND) as 68% of patients received Sentinel lymph node dissection as the initial axillary procedure. The practice of one surgeon (WJT) was completely analyzed and compared to the AD. 59 procedures were entered and the only incongruent practice was related to immediate reconstruction after mastectomy with a rate of 44% compared to 8% in the AD (p=0.0002). Conclusion. The Alberta Web SMR is the ideal vehicle for surgeon generated short term outcomes and is the future by which we will generate meaningful, valid and precise outcomes.

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Merkel Cell Carcinoma: The Role of Sentinel Lymph Node Biopsy and Adjuvant Radiation E.S. Ong,* M.G. Schlieman, W. Tan, G.E. Wilding, J.M. Kane. *Roswell Park Cancer Institute, Buffalo, NY.*

Introduction: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a high rate of locoregional recurrence. Early detection of nodal metastases with sentinel lymph node biopsy (SLNB) and locoregional adjuvant radiation (XRT) may improve locoregional control. Methods: Retrospective review of 57 MMC patients treated from 1980-2006. Data on patient and tumor characteristics, treatment, and survival were analyzed. Median follow up was 33 months (range 3-169 months). Disease-free survival (DFS) and overall (OS) were calculated by Kaplan-Meier, observed subgroup differences by log-rank test, and the Cox proportional hazard model for multivariate analysis. Results: Median age was 73 years (range 25-93 years) and 60% were male. Primary tumor site was 49% (28) head and neck, 39% (22) extremity and 12% (7) trunk. Clinical stage at presentation was 79% (45) stage I, 16% (9) stage II, and 5% (3) stage III. For stage I, 38% (17) underwent SLNB: 18% (3) were positive, 18% (3) were false negative, and 64% (11) were truly negative. In the 11 patients with a true negative SLNB, all remained disease-free at a median follow up of 55 months. For the 9 clinical stage II patients, all underwent dissection of the positive nodes and all recurred (3 nodal and 6 distant). For stage I/II patients, 48% (26) were treated with surgery alone, 48% (26) with surgery/adjuvant XRT, and 4% (2) with XRT alone. Five year DFS and OS for the entire group were 30% and 49%, respectively. Five year DFS was 54% for adjuvant XRT vs. 6% for no XRT (p=0.0001). At last follow-up, 63% (34) patients had recurred, 19 of which were dead of disease. On multivariate analysis, early stage and adjuvant XRT were associated with improved DFS (p<0.05). Stage of disease was the only variable associated with OS. Conclusions: The majority of MMC patients will develop recurrent/metastatic disease. Negative SLNB provides some staging/prognosis information as most patients with nodal disease relapsed. The false negative rate for SLNB was higher than for other cancers. Adjuvant XRT is associated with improved DFS but not OS.

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Neoadjuvant chemotherapy for adult extremity soft tissue sarcomas

S. Aguiar,* F.O. Ferreira, B.M. Rossi, W.T. Nakagawa, J.V. Salvajoli, D.L. Gimenez, A. Lopes. *Department of Pelvic Surgery, A.C. Camargo Cancer Hospital, Sao Paulo, Sao Paulo, Brazil.*

Introduction: treatment of soft tissue sarcomas (STS) is characterized by high rates of local control and limb sparing, but poor overall survival because of distant relapses and high rates of wound complications, when preoperative radiation is used. The objective of this study is to test the effectiveness of a protocol with neoadjuvant chemotherapy for STS. Methods: a phase II single-arm prospective trial was carried out. Only adult patients with high grade extremity lesions and tumors deep and larger than 5 cm were included. The protocol used 4 cycles of doxorubicin (30 mg/m2) and ifosfamide (2.0 mg/m2), followed by surgery. Radiation was given after surgery. Toxicity was classified by the NIH Toxicity Criteria and response was determined by the RECIST criteria. The others outcomes were the amputation and the wound-related complication rates. Results: between January, 2005 and December, 2006, 15 patients were included. The most common histological types were synovial sarcoma (40%), pleomorphic sarcoma (26.7%) and leiomyosarcoma (20%).The median size of the tumors were 15 cm (range from 6 to 30 cm). Eleven patients have completed the 4 cycles. Two patients have interrupted the protocol after 2 cycles because of toxicity and the others 2 patients have stopped chemotherapy after 2 cycles because of progression of disease and received preoperative radiotherapy. Ten patients (66.6%) had grade 3 and 4 toxicity, but no death related to treatment had occurred. Between severe complications, febrile neutropenia was the most frequent. By using the RECIST criteria, we observed 3(20%) cases of progression, 7(46.7%) cases of stable disease, and 5(33.3%) partial responses. No complete clinical or radiological response was observed. In the pathological analysis of the surgical specimens, 2(13.3%) cases had showed no residual disease (complete pathological response). The amputation rate was 6.7% (1 case) and complications related to the wound were observed in 2 cases (13.3%). Conclusions: the protocol was considered effective, as it showed a good rate of objective response, low rate of complications related to the operative wound, and maintained an acceptable amputation rate.

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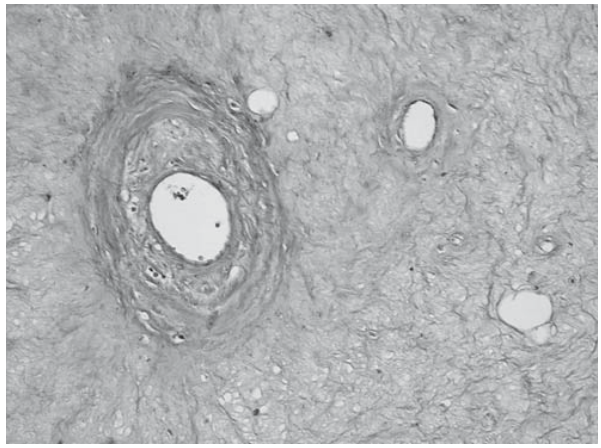
PREOPERATIVE RADIATED MYXOID LIPOSARCOMA

R.S. De Vreeze,* D. De Jong, R. Haas, F. Van Coevorden. *Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.*

Objectives: Myxoid liposarcoma (MLS) is a rare disease with a typical vascular "crow-feet" pattern unlike other subtypes of liposarcoma. Surgery and adjuvant radiotherapy (RT) has long been the standard treatment for most deep-seated sarcomas, but since the SR2 trial, which described similar local control for pre versus postoperative RT, a change in the sequence of these modalities is under discussion. The subgroup of MLS receiving preoperative RT was highly radiosensitive, but the explanation for this phenomenon is unknown. Here we describe results with preoperative RT and propose a mechanism explaining the high sensitivity of MLS based on its distinctive vascularization pattern. Methods: Between 1977-2006, 331 liposarcoma patients were treated at our institute. We reviewed all MLS cases that received preoperative RT. Results were compared to a matched control group of patients with other sarcoma classes receiving preoperative RT at our institute in the same period (2002-2006). Resected specimens from both groups were histologically compared, focusing on vascularization patterns. Results: Most tumors were intermediate grade (n=20), the remaining sarcomas were high grade (n=11). In eight out of ten MLS patients a pathological complete remission (pCR) was found after preoperative RT. In the control group (n=21), no pCR was found, although sarcomas with myxoid-like branching stromal vasculature had a near pCR. Histology of highly responding specimens in both groups contained a substantial damage to the endothelium of medium sized arterioles with hypertrophy of vascular structures and parietal thrombus formation. Furthermore uniform oval shaped mesenchymal areas and a qualitative as well as a quantitative decrease of nuclei were seen. Conclusions: Based on our findings we suggest offering MLS patients preoperative RT. Remarkably, there is a trend for sarcomas with myxoid-like branching vasculature to be similarly radiosensitive. It is likely that the effect of RT on the specific vascularisation explains this observation. Both preoperative radiotherapy and reduction of radiation dose gains probably advantages in case of myxoid-like sarcomas but this needs more study.



MLS arteriole after preoperative radiotherapy

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Diagnostic accuracy of FISH and RT-PCR in 50 routinely processed synovial sarcomas

S.T. Heuvel,[1]* H.J. Hoekstra,[1] A.J. Suurmeijer.[2] *1. Department of Surgery; University Medical Center Groningen, Groningen, Netherlands; 2. Department of Pathology; University Medical Center Groningen, Groningen, Netherlands.*

Background: Molecular detection of SYT-SSX fusion genes is the most reliable tool for diagnosing synovial sarcoma (SS). The objective of this study was to investigate the accuracy of RT-PCR and a commercially available FISH technique for formalin-fixed and paraffin-embedded (FFPE) tumor tissue. Patients and Methods: Fifty tumors with typical SS histology and 12 histologic mimics of SS were included. RT-PCR for SYT-SSX1/SSX2 gene fusions and FISH analysis for SYT gene breaks were performed on these 62 FFPE tumors. Results: All 50 SS were positive by either RT-PCR or FISH. Forty-seven SS (94%) were true positive by RT-PCR and 41 SS (82%) were true positive by FISH. FISH and RT-PCR results were interpretable and concordant in 38 cases (76%). Two cases were not interpretable by RT-PCR and 6 cases were not interpretable by FISH. One SS was false-negative with RT-PCR and three SS were false-negative with FISH. RT-PCR and FISH had a sensitivity of 94% and 82%, a specificity and positive predictive value of 100% and 100% and a negative predictive value of 80% and 75%, respectively. Conclusion: RT-PCR had a higher sensitivity than FISH. One of both methods was always positive, whereas both methods were concordant in 76% of cases. From an economic point of view, we advocate to use FISH as a method of first choice, because it allows microscopic control of a true positive result (unpaired fluorescent signals in a break apart assay). Using this approach, 80% of SS can be diagnosed by FISH only and 20% would need to be confirmed by RT-PCR.

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Characterization of PDGF α/β and PDGFR α/β Expression in Dermatofibrosarcoma Protuberans: Implications for Targeted Molecular Therapy

A. Meguerditchian,* F. Samie, M. Vaughan, R. Cheney, N. Zeitouni, J.M. Kane III. *Roswell Park Cancer Institute, Buffalo, NY.*

INTRODUCTION Dermatofibrosarcoma protuberans (DFSP) is associated with the chromosomal translocation t(17;22)(q22:q13), producing fusion of the collagen 1a1 gene promoter to the PDGFβ oncogene. This is postulated to continuously activate PDGFRβ, a known clinical target for the tyrosine kinase inhibitor imatinib mesylate (IM). As up to one third of DFSP do not highly express PDGFRβ and are excluded from IM therapy, we questioned whether or not PDGFRα may alternatively be highly expressed. METHODS Using standard antigen retrieval protocol, paraffin-embedded primary DFSP tumors from 17 patients treated at a single institution were stained using polyclonal anti-PDGFβ, anti-PDGFRβ, anti-PDGFα and anti-PDGFRα antibodies. Staining was assessed for percentage and intensity by an independent pathologist . Percentage of staining was

graded semi-quantitatively: >75%, 50-75%, >50%, 25-50% or 0%. "High expression" was defined as ≥ 50% of tumor cells staining positive. Intensity was graded as strong (3+), moderate (2+), or weak (1+). RESULTS Staining was performed/interpreted in all 17 DFSP tumors. All tumors had a high expression of PDGFβ with 88% (15/17) graded as moderate or strong intensity. In contrast, only 12% (2/17) tumors highly expressed PDGFRβ and their intensity was weak. For PDGFRα, 82% (14/17) tumors had high expression with 70% (10/14) having moderate or strong intensity. For completion, PDGFα had high expression in 88% (15/17) with 87% (13/15) having moderate intensity. A representative tumor stained for PDGFβ, PDGFRβ, and PDGFRα is shown in figure 1. CONCLUSION: As expected, given the known chromosomal translocation, high expression of PDGFβ was observed in all DFSP tumors but its corresponding receptor (PDGFRβ) was not concomitantly highly expressed. In contrast, PDGFRα was highly expressed in 82% of tumors. Given that PDGFβ may cross activate PDGFRα and this receptor isoform can also be inhibited by IM, high PDGFRα expression even in the absence of PDGFRβ expression may expand clinical eligibility for IM therapy in DFSP.

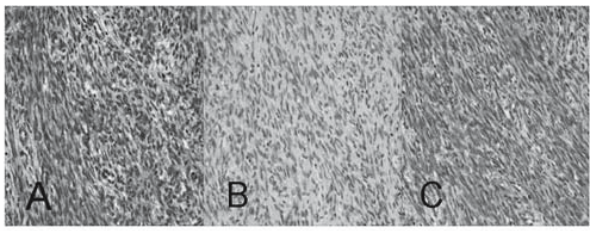

Figure1: Representative immunohistochemical staining of a DFSP specimen for: A) PDGFβ 20x; B) PDGFRβ 20x; C) PDGFRα 20x

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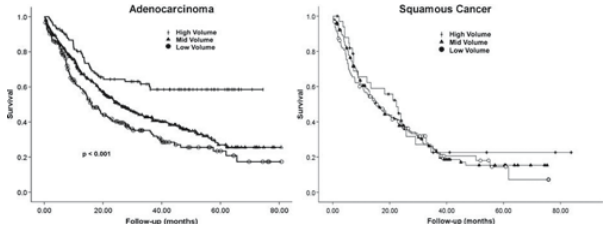
Esophageal Cancer: No Benefit for African American Patients Treated at High Volume Centers D. Franceschi,* L. Koniaris, A. Livingstone. *University of Miami, Miami, FL.*

Background: Patients with esophageal cancer operated at high volume centers have improved outcome. The volume-effect impact on long term survival for all patients with esophageal cancer is unknown. We sought to define the benefit of treatment center volume, cancer type and race on long term outcomes for esophageal cancer. Methods: Incident esophageal cancers diagnosed from 1998 to 2002 in Florida were examined using linked statewide cancer registry, inpatient, and outpatient data. Centers were divided into high volume (> 20 patients/year, n = 4), mid volume (5 – 19 patients/year, n = 51) and low volume (< 5 patients/year, n = 204) groups. Results: Overall, 5098 cases were identified. Mean age was 68 years (range 21 – 102). Patients treated at high volume centers had a significantly improved long-term survival of 13.7 months versus 9.8 and 9.3 months for middle and low volume centers ($p < 0.001$). This effect was mostly caused by benefits seen in resected patients with adenocarcinoma of the esophagus (13% of total), where median survival was > 60 months for high volume versus 25.8 months and 16.1 months for mid and low volume centers ($p < 0.001$) - see figure. No impact of volume on outcome was seen for non-surgical cases or operated patients with squamous carcinoma. In addition to age, race and undergoing surgery, volume-effect was an independent predictor of improved survival after adjusting for comorbidities (adjusted hazard ratio 0.79, 95% CI = 0.70-0.89). Squamous histology's negative impact disappeared on multivariate analysis when adjusted for race. Conclusions: Treatment center volume remains associated with a dramatically improved long-term survival for patients with esophageal cancer. This benefit however has not been extended to African American patients. This appears to be multifactorial and include both late presentation and a high fraction of squamous carcinoma.



Survival of Operable Esophageal Cancer by Center Volume

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Epidemiologic Trends for Esophageal Cancer E.T. Sevensma,[2]* E.J. Kort,[3] T.L. Fitzgerald.[1] *1. Richard J. Lacks Cancer Center, Department of Surgical Oncology, Grand Rapids, MI; 2. Ingham Regonal Medical Center, Lansing, MI; 3. Van Andel Reasearch Instutute, Grand Rapids, MI.*

Introduction: Over the last three decades there has been a marked increase in the incidence of esophageal carcinoma. In order to better define this trend we reviewed the epidemiology of esophageal carcinoma in a statewide tumor registry. Methods: All cases of esophageal carcinoma from 1986-2002 were identified in the State of Michigan tumor registry. This information was paired with Michigan census data to determine the incidence per 100,000 people per year and categorized based on sex and race. R statistical analysis framework (Ihaka) was used for analysis and a p value of < 0.05 defined as significant. Results: A total of 7,308 cases of esophageal carcinoma were identified over the study period, 3,526 adenocarcinoma and 3,782 squamous cell cancers. There was a significant overall increase in the incidence of esophageal cancer, 4.13 to 4.77. However, the rate of squamous cell cancer significantly decreased from 2.91 to 1.80. Adenocarcinoma occurred most commonly in whites, 97%, and was most frequent in the distal esophagus. There was a 3-fold increase in adenocarcinoma incidence white male and females; 0.30 to 0.98 and 2.51 to 5.88. A smaller, but also significant, increase was seen in black male (0.35 to 0.71) with no change for black women. Conclusions: There has been a marked increase in the incidence of esophageal cancer adenocarcinoma. This mirrors the epidemic increase in obesity and GERD in Michigan, however, the race and gender differences suggests that this in not the sole mechanism.

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High rate of pathologic complete response after neoadjuvant high-dose radiotherapy and cisplatin in NSCLC of the superior sulcus I. Kappers,* J. Burgers, J. Belderbos, J. Van Sandick, N. Van Zandwijk, H.M. Klomp. *The Netherlands Cancer Institute- Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.*

Introduction: Complete en-bloc pulmonary resection with thoracic wall is the main step towards local control and long-term survival for T3/T4 non-small cell lung cancer of the superior sulcus (Pancoast tumors). Preoperative (chemo)radiotherapy (CRT) can contribute to better local control and survival, but high-dose radiotherapy (>45Gy) is controversial in this setting. The aim of the present study was to evaluate the efficacy and safety of an concurrent induction CRT protocol of 66 Gy with cisplatinum preceding surgery. Methods: Patients with Pancoast tumors stage II-III, referred between 1996 and 2006, were reviewed retrospectively. The preferred induction regimen was concurrent CRT (66 Gy in fractions of 2,75 Gy with daily cisplatinum 6 mg/m2). Surgical resection was planned 5-7 weeks after completion of CRT. Results: 85 patients with Pancoast tumors, 57 men and 28 women, were referred. Follow-up ranged from 9-123 months. Mean age was 57 years (32-82). Twenty-five patients had stage IIB (29%), 7 stage IIIA (8%), 32 stage IIIB (38%) and 21 stage IV (25%). Of those patients pre-

senting with stage II or III disease, 37 medically operable patients with potentially resectable tumors received induction therapy. After restaging, 22 patients underwent resection. All these resections were complete and local recurrences were not observed. In 13 out of 22 patients a pathologic complete tumor response (pCR) was found after induction treatment. pCR was a prognostic factor for survival (5 year survival of 50% vs. 17%). Pathologic response was not evident from CT or MR imaging. The morbidity of surgery after induction treatment was acceptable: 6 pneumonias, 1 tracheoesophageal fistula, 1 chylothorax, 1 complete atelectasis, 1 postoperative bleeding. There were no fatal toxicities or treatment-related mortalities. The 2- and 5-years overall survival was 70% and 37%, respectively. Conclusions: This concurrent induction scheme of high-dose radiation with cisplatinum was effective with a pCR rate of 56% in operated patients. Surgical resection following induction with concurrent CRT was associated with acceptable morbidity and excellent local control.

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Radiation Resistant Prostate Cancer: A Single Institution Experience with Laparoscopic and Robotic Salvage Prostate Cancer Surgery M. Kawachi,[1]* R. Viterbo,[2] D. Josephson,[1] R. Nelson,[1] L. Crocitto,[1] J. Yoshida,[1] K. Chan,[1] T. Wilson.[1] *1. Urology, City of Hope, Duarte, CA; 2. Fox Chase Cancer Center, Philadelphia, PA.*

Purpose: To present our outcomes following laparoscopic and robotic assisted salvage prostatectomy. Methods: From April 2001 to September 2006, 20 consecutive patients with biopsy-proven prostate cancer following definitive radiotherapy underwent minimally invasive salvage prostatectomy. Salvage surgery was considered only if the patient had radiation resistant disease, did not have diagnostic evidence of systemic disease and had a life expectancy of greater than 10 years. Patients were classified as radiation resistant if it had been more than 2 years since the completion of their radiation therapy, if they had biopsy-proven persistent disease, and if there was biochemical evidence of disease progression (i.e. increasing PSA). Age, race, type of radiation (permanent/temporary seeds, conformal/intensity modulated EBRT, or proton beam), or concomitant use of hormone therapy during radiation were not considered strict exclusion criteria. Assessment of post-surgical clinical and functional parameters, including morbidity, is included in this report. Results: Of the 20 patients who underwent salvage prostatectomy, 11 had an LRP and 9 had an RAP. Median PSA was 6.7 (range 1.1 to 11.1), median operating time was 228 minutes (range 102 to 354), average blood loss was 200 cc (range 150 to 600), median Gleason score was 7 (range 6 to 9), and median specimen weight was 46 grams (19 to 70). Positive surgical margins were present in 2 of 20, seminal vesicle invasion in 1 of 19 and extra capsular extension in 4 of 20. Pathologic staging ranged from pT2a to pT4. There was no conversion to open surgery. No death or intraoperative complications occurred, nor was any patient transfused postoperatively. Median postoperative stay was 3 days (range 2 to 10). Prostate specific antigen recurrence was lower than 0.1 ng/ml in 15 of the 20 patients. Conclusion: While radiation resistant prostate cancer continues to represent an infrequent but challenging oncologic problem for patients and practitioners, the short-term results of our application of LRP or RAP procedures in radiation resistant patients is promising and warrants continued investigation.

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Urologic Complications of Resection Following Combined Modality Treatment of Advanced Pelvic Cancers K. Moozar,[2]* R.S. McLeod,[1] Z. Cohen,[1] H. MacRae,[1] N.E. Fleshner,[2] C.J. Swallow.[2] *1. Mount Sinai Hospital, Toronto, ON, Canada; 2. Princess Margaret Hospital, Toronto, ON, Canada.*

Background: The perception among surgeons is that preoperative radiation increases the incidence of urologic complications following composite resection, but there is little evidence to support or refute this claim. Methods: Patients with ureteric reconstruction as a component of en bloc resection of pelvic tumors were identified from an institutional database (1982-2007). Patients with colorectal and anal maligancies or pelvic sarcoma were included; primary GU tumors or simple partial cystectomies were excluded. Charts were reviewed to determine the incidence, nature and management of urologic complications. Demographic and treatment-related variables were assessed in association with urologic complications. Results: 79 patients (28 female, 51 male) met the inclusion criteria. Median age was 57 (range 30 – 85). The primary was a carcinoma of the rectum in 51 (65%), colon in 12, anus in 6, and a sarcoma in 10 patients. Treatment was for locally advanced primary in 38 (48%) and for recurrence in 41 (52%). Pelvic exenteration was performed in 81%. Serious urologic complications requiring intervention were observed in 27% (n=21). These included 12 anastomotic strictures, 8 anastomotic leaks, 2 fistulae, 2 ileal stoma stenoses and 2 renal failures (5 patients had more than one complication). Fourteen cases were managed nonoperatively, but 7 required surgical revision including three nephrectomies. Overall, 75% (n=59) of patients received pelvic radiation prior to the index surgery. The majority of planned neoadjuvant therapy included concomitant infusional 5-FU. The rate of urologic complications was similar in patients who had received radiation vs. those who had not (29% vs 25%, respectively, p=0.11, Chi square). Conclusion: 27% of patients who underwent ureteric resection and reconstruction during composite resection of advanced pelvic tumors developed a urologic complication that required intervention. Preoperative chemoradiotherapy did not predispose patients to urologic complications. Optimization of surgical technique at the time of en bloc resection may obviate the need for subsequent revision, which was required in one third of those with complications