Objective: To identify gene expression alterations which occur in HNSCC in response to primary treatment. Methods: All patients were participants in a previously established, IRB approved study to assess gene expression patterns in head and neck cancer patients. Surgical biopsies were obtained from the primary site of twelve patients with HNSCC at the time of initial diagnosis. A second sample was also taken from the recurrent, or persistent, tumor in these patients after failure of initial therapy. Total RNA [miRNA] was extracted and amplified by T7 linear amplification. Amplified RNA was fluorescently labeled and hybridized to microarrays containing 27,323 cDNA clones. For each patient, the primary tumor from an individual patient (Cy3-green) was directly compared to the corresponding recurrent or persistent tumor of that patient (Cy5-red). Results were analyzed to identify consistent differences in gene expression between primary tumors and their recurrence or persistence. Results: Twelve patients with messenger RNA extracted from both their primary tumor and the recurrent or persistent tumors were included. Six patients had larynx cancer, 5 had cancer of the pharynx, and 1 had an oral cavity primary. Three patients underwent surgery alone as their primary treatment, and four patients received surgery and radiation. Four received concomitant chemotherapy and radiation, and one patient received preoperative surgery with postoperative chemotherapy and radiation. Using a cutoff of 1.8-fold fluorescence ratio to define differential gene expression, 58 genes were found to be downregulated, and 27 were found to be upregulated, in at least seven of the twelve patients. An additional 122 genes were generated for the upregulated group when the limit was extended to at least six patients. The products of these genes can be grouped into several functional categories, including cell adhesion molecules, immune modulators, and cell cycle regulators. Three genes in particular, COX2, MMP-3, and ADAM12 were identified by our study. Analysis with tissue microarrays is underway. Conclusions: Treatment of HNSCC can result in changes in gene expression. We have identified several genes that were frequently upregulated or downregulated in recurrent or persistent HNSCC tumors. Some groups have implicated several of these genes in potential treatment resistance. Further investigation is needed to determine if the significance of the other genes is yet to be determined. Many of the genes that we have identified have not been previously described in recurrent or persistent head and neck squamous cell carcinoma. Further exploration may provide new biologic markers for tumor staging and recurrence, as well as novel targets for therapy. S002: DIFFERENTIAL EXPRESSION OF MiCRORNA’S IN HEAD AND NECK SQUMOUS CELL CARCINOMA CANCER STEM CELLS S. Joshua, L.E. Allens1, Y. Shimo no1, M.F. Clark1, M. Wong2, J.L. Weissman1, M.J. Kaplan1, Stanford University School of Medicine, Stanford, CA; 2National University of Singapore, Singapore, Singapore

Objective: A subpopulation of CD44+ cells with cancer stem cell (CSC) properties was previously identified by flow cytometry in head and neck squamous cell carcinoma (HNSCC). There is increasing evidence that microRNAs (miRNA) play a major role in cancer. These 21-23 nucleotide molecules, processed from larger endogenous pre-miRNA and not translated into proteins, silence gene expression post-transcriptionally. They can act both as oncogenes and tumor suppressors depending on whether they silence a transcription activator or a suppressor. The purpose of this study was to assess differences in the miRNA expression profiles between the CD44+ and CD44- subpopulations. Methods: Fresh HNSCC samples were digested and cells sorted into Trizol to obtain CD44+ and CD44- subpopulations, as previously described. The differential expression was tested using real time PCR. Three samples were screened for 460 miRNAs. Thirty miRNAs demonstrating initial consistent differential expression were then further evaluated in eight additional samples. Potential proteins targeted by the miRNAs were searched via Targetscan [www.targetscan.org] and Pictar [http://pictar.bio.nyu.edu/]. Results: MiR-18b and miR-210 were under expressed in the CD 44+ cells. MiR-127, miR-409-3p and miR-497 were over expressed in the CD44+ population. Conclusions: MiRNAs appear to be differentially expressed in a putative HNSCC stem cell population. This offers further impetus to study specifically the CD44+ subpopulation that appears to include a cancer stem cell population. Additional corroborative and functional studies are planned.
xeroderma pigmentosum protein group A (XPA), Py-glycoprotein (MDR1) and multidrug resistance-associated protein 2 (MRP2). Unvariable and multivariable proportional hazard analyses were performed to investigate associations between each individual marker and outcome. In addition, the global test was used to test all variables simultaneously and selected combinations of markers for an overall association with local control. Results: Univariable proportional hazard models showed statistically significant increased relative risks of RB, P16 and MRP2 for local control and MDR1 and HIF-13B1 for overall survival. MRP2, MDR1 and P16 levels were positively associated with outcome whereas RB and HIF-1 had a negative relationship. Using Goeman’s global testing no combination of markers was identified that was associated with local control. Grouping the markers according to their function revealed an association between a combination of three markers [P16, P21, and P27] and outcome (p=0.03) was found. After the multivariable analysis MRP2 and RB remained significant independent predictive markers for local control. Conclusions: This study describes the possible prognostic value of 18 biomarkers for the outcome in patients uniformly treated with concurrent chemoradiotherapy. MRP2 and RB were found to be associated with outcome in patients treated with concurrent chemoradiotherapy.

SO05: CORRELATION OF P16 STATUS, EGFR AND CYCLIN D1 EXPRESSION WITH PATHOLOGIC NODAL STATUS IN HEAD AND NECK CANCER

Objective: To determine correlation between presence of nodal metastases in head and neck squamous cell carcinoma (HNSCC) and alteration of tumor suppressor genes p16, EGFR and cyclin D1. Methods: 33 HNSCC frozen samples acquired from previous surgery in subjects with both clinical and pathologic negative nodal (pN0) status were analyzed via RT-PCR and direct sequencing methods for alterations in the p16 tumor suppressor gene (absent expression or mutation) as well as real-time PCR for quantitative expression levels of p16, EGFR, and cyclin D1. For comparison, a second group of 33 HNSCC samples (matched for tumor site) from subjects with pathologic positive nodal status (pN+) was similarly analyzed. Results: In the entire group of HNSCC samples analyzed (66 samples) p16 alteration (absent expression or mutation) were detected in 42 specimens (63%). p16 alterations were identified in higher proportion of HNSCC samples in the group with pathologic positive nodal status compared to the group with pathologic absence of nodal disease (76% vs 52%, p = 0.04). Types of p16 alteration observed were similar between pN0 and pN+ groups. Absence of p16 expression was the most common alteration detected (33 of 42, 78.6%) followed by single base pair alterations (11.9%) and large exon 2 deletions (9.5%). Assessment of quantitative expression levels of p16, EGFR, cyclin D1 via real-time PCR is currently underway. Conclusions: The observed frequency of p16 alteration was similar to evidence higher in subjects with pathologic positive nodal status indicating possible prognostic clinical relevance. As such, p16 along with other markers currently being analyzed may play a role in future risk-based molecular profiling of HNSCC to guide therapy decisions.

SO06: DECREASED GAMMA-CATENIN EXPRESSION IS ASSOCIATED WITH POOR SURVIVAL IN T1 AND T2 TUMOURS IN ORAL SQUAMOUS CELL CARCINOMA

Background: Increased expression of the cadherins and catenins are important factors in intercellular adhesion. The aim of this study was to investigate whether decreased expression of catenins is an independent risk factor for poor survival in oral squamous cell carcinoma (OSCC). Methods: This study included a retrospective cohort of 124 OSCC patients. Clinicopathological data was recorded and the patients were followed up on a regular basis. Using immunohistochemical staining the sections were stained with 020alpha-, beta- and gamma-catenin antibodies. The staining was then classified based on the fraction of tumor cells in the sample with membranous staining. For statistical analysis the material was divided into two subgroups. X2 -test and Kaplan Meier was used to evaluate the prognostic value of catenin expression in different OSCC patient groups. To determine whether gamma-catenin expression in the primary tumor can be used to predict clinical outcome in node negative or node positive patients as well as in small tumours we compared the disease specific survival in different groups. Results: The number of patients was 124. Forty patients were stage I (33%), 36 stage II (29%), 24 stage III (19%) and 24 stage IV (19%). Mean age was 62 years. Mean follow-up time was 52.2 months (0.6-271.6). In Kaplan-Meier survival analysis gamma-catenin (p=0.004) but not alpha- or beta-catenin (p=0.247 and p=0.86, respectively) correlated independently with poor disease-specific survival. 29 of the patients presented with neck metastasis (23%), 70% of the patients with decreased gamma-catenin expression had neck metastasis. Meanwhile only 9/29 (31%) patients had neck metastasis if the gamma-catenin expression was normal (p<0.025). There were altogether 92 patients with small T1 and T2 OSCC. Sixteen of these 92 (17%) patients had died during the follow up if the gamma-catenin expression was reduced, while in the normal expression group only 7 had died (8%)(p<0.02). In bigger T3-4 tumours no impact on survival was found (p=0.268). Conclusions: In general, prognosis of oral cancer declines with higher tumour stage and grade. However, in certain cases clinical outcome can be poor even in stage I primary tumours. In this study we show that reduced gamma-catenin expression correlates independently with poor survival in OSCC. Furthermore, reduced gamma-catenin expression correlates with positive nodal status and poorer survival even in small T1 and T2 tumours. These data suggest that gamma-catenin expression could be used as a prognostic factor for OSCC, when planning appropriate treatment option for individual OSCC patients.

SO07: PREVALENCE OF MGMT METHYLATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA AND IMPACT ON CLINICAL OUTCOMES

Background: The O6-methylguanine-DNA methyltransferase (MGMT) gene encodes a specific DNA repair enzyme that protects cells from toxicity of alkylating agents. Thus, MGMT activity is a major mechanism of resistance to alkylating drugs. It has been shown that decreased MGMT gene expression by promoter hypermethylation results in improved survival in patients with certain types of tumors that are treated with alkylating chemotherapeutic agents. Objectives: To determine the prevalence of MGMT methylation in patients with locally advanced HNSCC treated with chemoradiotherapy with/without surgery and to evaluate the impact of this methylation on loco-regional control, as well as overall and disease free survival. Patients and Methods: Out of 428 consecutive patients treated with chemo-radiation therapy in our institution and followed for a median of 37 months, 199 paraffin embedded biopsy or surgical specimens were retrieved. DNA was extracted and subjected to bisulfite treatment. A methylation specific PCR (MSP) was conducted to assess the methylation status of the MGMT gene promoter. Statistical analysis was performed using Fisher’s test for categorical data and Kaplan-Meier’s curves and log-rank statistics for failure times. Results: From the initial 199 DNA extracts, 177 (89%) were successfully modified with bisulfite. Out of these, 71 (40%) demonstrated hypermethylation of MGMT. For MGMT methylation cases and non-methylation cases, patients characteristics were not statistically different. LCR was respectively 87 and 77% (p=0.26), DFS was 80 and 60% (p=0.38), distant metastasis free survival was 92 and 78% (p=0.08) and OS was 64 and 62% (p=0.99) at 3 years. Conclusions: MGMT methylation status is highly prevalent and may influence overall response to chemoradiation therapy in patients with advanced stage HNSCC. More complete results and analysis will be presented at the meeting.

SO08: AKT ACTIVATION IN HNSCC PREDICTS SURVIVAL AND CORRELATES WITH HPY STATUS

Background: Akt is an important serine-threonine kinase, which regulates cell proliferation, survival, invasion and metabolism. We have previously shown that Akt is highly activated in HNSCC and is associated with poor survival. Here, we aimed to determine if Akt activation is an independent predictive marker for head and neck cancer survival and if it could be used to predict survival in patients with HPV-related HNSCC. Methods: The complete results and analysis will be presented at the meeting.

SO09: PREVALENCE OF MGMT METHYLATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA AND IMPACT ON CLINICAL OUTCOMES

Background: The O6-methylguanine-DNA methyltransferase (MGMT) gene encodes a specific DNA repair enzyme that protects cells from toxicity of alkylating agents. Thus, MGMT activity is a major mechanism of resistance to alkylating drugs. It has been shown that decreased MGMT gene expression by promoter hypermethylation results in improved survival in patients with certain types of tumors that are treated with alkylating chemotherapeutic agents. Objectives: To determine the prevalence of MGMT methylation in patients with locally advanced HNSCC treated with chemoradiotherapy with/without surgery and to evaluate the impact of this methylation on loco-regional control, as well as overall and disease free survival. Patients and Methods: Out of 428 consecutive patients treated with chemo-radiation therapy in our institution and followed for a median of 37 months, 199 paraffin embedded biopsy or surgical specimens were retrieved. DNA was extracted and subjected to bisulfite treatment. A methylation specific PCR (MSP) was conducted to assess the methylation status of the MGMT gene promoter. Statistical analysis was performed using Fisher’s test for categorical data and Kaplan-Meier’s curves and log-rank statistics for failure times. Results: From the initial 199 DNA extracts, 177 (89%) were successfully modified with bisulfite. Out of these, 71 (40%) demonstrated hypermethylation of MGMT. For MGMT methylation cases and non-methylation cases, patients characteristics were not statistically different. LCR was respectively 87 and 77% (p=0.26), DFS was 80 and 60% (p=0.38), distant metastasis free survival was 92 and 78% (p=0.08) and OS was 64 and 62% (p=0.99) at 3 years. Conclusions: MGMT methylation status is highly prevalent and may influence overall response to chemoradiation therapy in patients with advanced stage HNSCC. More complete results and analysis will be presented at the meeting.

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way in HPV-positive and HPV-negative HNSCC. 

**Methods:** The PI3K/AKT pathway was examined in forty primary HNSCC (20 HPV+, 20 HPV-) using various techniques including immunoblotting, fluorescent in situ hybridization, reverse transcription real time PCR, and direct sequencing for mutation analyses. 

**Results:** Our quantitative immunoblot data revealed that phospho-AKT was increased in HPV-negative tumors relative to HPV-positive HNSCC. Similar results were observed using the phospho-AKT:total AKT ratio. High phospho-AKT levels correlated with worse survival, and with HPV-negative tumor status. Low phospho-AKT levels and HPV-positive status correlated with one another and with improved survival. AKT kinase is implicated in many aspects of tumorigenesis, including cell growth, proliferation, motility, survival and apoptosis. The major activator of AKT is PI3K. Interestingly, we observed low-level amplification of the gene encoding the catalytic subunit of PI3K, PIK3CA gene, and modestly higher expression of p110b31 in HPV-negative samples. Additionally, all mutations of PIK3CA within this cohort were seen in HPV-positive HNSCC. 

**Conclusion:** These data show that low AKT activation is associated with HPV-positive HNSCC and better survival suggesting that AKT activation may be a molecular marker of poor outcome in HNSCC. Additionally, our data show that PIK3CA expression and/or mutation are not responsible for AKT activation in HPV-negative HNSCC suggesting that alternative mechanisms of AKT activation are utilized in HPV-negative tumors.

**SO09: PROTEIN KINASE CK2 SUBUNITS DIFFERENTIALLY REGULATE TRANSCRIPTION FACTORS AND TARGET GENES IMPLICATED IN THE HEAD AND NECK**

**M.S.Brown1, Q.Dial1+2, A. Pattathiyil1, C. Allen1, Z. Czep2, C. Van Vaeke2, N. HD and CRT/PhRizer, Bethesda, MD; 2N. HD, Bethesda, MD**

**Objective:** Protein Kinase CK2 (formerly casein kinase II) is a ubiquitous serine/threonine kinase implicated in several malignancies including head and neck squamous cell carcinoma (HNSCC). CK2 is a tetrameric protein comprised of 2 α or α′ catalytic subunits and 2 β regulatory subunits, that can phosphorylate a variety of intermediate kinases, transcription factors, apoptotic and tumor suppressor proteins. Our laboratory has previously shown that CK2β is essential for activation of transcription factor NF-κB, and that recombinant CK2a phosphorylates IKKβ involved in the activation of IkB-α and NF-κB. However, the effects of different CK2 subunits on this and other molecular mediators of the malignant phenotype of HNSCC have not been delineated. In this study, the expression of different CK2 subunits was analyzed in a panel of HNSCC (UM-SCC) cell lines, and the role of specific CK2 subunits on gene expression, tumor cell growth and migration were investigated. 

**Methods:** Basal gene expression of CK2 subunits in 10 UM-SCC cell lines was determined using quantitative RTPCR, and compared to normal human keratinocytes (HEK293). Total protein levels of CK2 subunits, as well as their nuclear and cytoplasmic distributions were analyzed by Western blot analysis. CK2 kinase activity was assayed by the Cyclin-dependent Kinase Assay Kit. Specific knock-downs of CK2 subunits were performed using siRNA, and the effects on the downstream genes were analyzed by quantitative RTPCR. SiRNA-mediated biological effects on tumor cells were examined by MTT cell proliferation assays, migration assays, and DNA flow cytometry. 

**Results:** Over-expressed mRNA and protein levels were observed for each CK2 subunit in a panel of UM-SCC cells relative to HEK293 cells; and in tumor cells, the CK2α subunit was more abundant than the α′ subunit in the nucleus. Elevated CK2 kinase activity observed in tumor cells could be inhibited by CK2 inhibitor apigenin. SiRNA treatment of each subunit significantly knocked down the respective CK2 subunit at the mRNA and protein levels, and inhibited important NF-κB regulated downstream genes. Conversely, the gene expression of p53 tumor suppressor family members, p21, TAp73 and p73 were differentially regulated by knockdown of individual CK2 subunits. In addition, specifically knocking down the CK2α but not α′ or β subunits inhibited tumor cell proliferation and migration in culture. In addition, CK2 specific inhibitor apigenin and 2-dimethylamino-4,5,6,7-tetramethoxazole (DMAT) inhibited tumor cell growth by cell proliferation assay. 

**Conclusion:** Ablant over-expression and activation of CK2 contributes to HNSCC malignancy through its ability to drive expression of genes that govern cell cycle and tumor suppressors that promote apoptosis. CK2α was of greater functional importance as compared to the other subunits, consistent with its greater nuclear localization, suppressive effects on p53 family and gene expression, and its ability to promote cell proliferation and migration. Our study provides evidence that CK2, especially CK2α, is a potentially important therapeutic target for HNSCC.

**SO10: IMPACT OF 2002 AJCC GUIDELINES IN LYMPH NODE EVALUATION FOR WDTc**

**M.Evasovich1, E.B.Haberman1, A.A. Abraham1, L.Burmeister1, B.A.Virmig1, University of Minnesota, Minneapolis, MN**

**Objective:** The most recent 2002 AJCC/UICC TNM staging guidelines for thyroid cancer address nodal status and node location. Later, in 2006, the American Thyroid Association released guidelines (R27) recommending that surgical compartmental resection of cervical lymph nodes at the time of thyroid surgery to reduce the risk of recurrence and possibly mortality. The purpose of this study was to examine lymph node (LN) status in patients with well-differentiated thyroid cancer (WDTc) as it relates to tumor size, nodes examined and surgical management. 

**Methods:** Retrospective cohort analysis using Surveillance, Epidemiology, and End Results (SEER) cancer registry data between years 1992-2004. The cohort was divided into Group A: 1992-2001 and Group B: 2002-2004; after release of 2002 AJCC guidelines. Histology was limited to papillary and follicular thyroid cancers (WDTc) from eleven continuous registries. The Wilcoxon two-sample T test, chi-squared analysis, and Cochran-Armitage Trend test were used to compare trends of nodes sampled and status over time. 

**Results:** From 1992-2004, 30,477 patients with WDTc were reported in SEER data. Of those, 12,084 (39.7%) patients had at least one node sampled for pathology. 49.8% (6016) were node negative compared to 50.2% (6057) node positive. Node assessment over time remained clinically unchanged (but because of patient number was statistically significant) at 39.6% in 1992 and 40.7% in 2004 (p<0.001). Overall tumor size did not predict nodal sampling but was associated with node positivity (p<0.001). 

**Conclusion:** The 2002 AJCC/UICC classification system emphasizing nodal status, has not changed the approach to lymph nodes in WDTc. Less than half of the patients with WDTc have nodes sampled; questioning adequate staging. Even with small tumors (<1.0cm) one-third of the patients have positive nodes. This data supports nodal sampling for recurrent/persistent Papillary Thyroid Cancer undergo sampling but was associated with node positivity (p<0.001). Table A of Group A 38.8% and Group B 41.6% of patients with WDTc had nodes sampled. The mean number of nodes sampled increased slightly from 5.7 to 6.3 between the two groups but percent of positive nodes decreased significantly from 52.9% in Group A to 44.5% in Group B (p<0.001); while the mean number of positive nodes remained stable (Group A: 1.96 positive nodes/nodes sampled, Group B: 1.90 positive nodes).

**Table A. Tumor size (cm) and Node Status**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Node Status</th>
<th>n=3138</th>
<th>n=6787</th>
<th>n=1049</th>
<th>n=1099</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1-1.0cm</td>
<td>Negative</td>
<td>1953</td>
<td>3306</td>
<td>427</td>
<td>330</td>
</tr>
<tr>
<td>1.1-1.4cm</td>
<td>Negative</td>
<td>1185</td>
<td>3481</td>
<td>622</td>
<td>769</td>
</tr>
<tr>
<td>&gt;4cm</td>
<td>Negative</td>
<td>(62.2%)</td>
<td>(48.7%)</td>
<td>(40.7%)</td>
<td>(30.0%)</td>
</tr>
<tr>
<td></td>
<td>Positive*</td>
<td>(37.8%)</td>
<td>(51.3%)</td>
<td>(59.3%)</td>
<td>(70.0%)</td>
</tr>
</tbody>
</table>

* (p<0.001); Excluding 11 cases with unknown node positivity

**Conclusion:** The 2002 AJCC/UICC classification system emphasizing nodal status, has not changed the approach to lymph nodes in WDTc. Less than half of the patients with WDTc have nodes sampled; questioning adequate staging. Even with small tumors (<1.0cm) one-third of the patients have positive nodes. This data supports nodal sampling for recurrent/persistent Papillary Thyroid Cancer undergoing lateral neck dissection.

**SO11: PATTERNS OF CERVICAL LN METASTASIS IN PATIENTS WITH RECURRENT/PERSISTENT PAPILLARY THYROID CANCER UNDERGOING LATERAL NECK DISSECTION**

**T.Y.Farroag1, R.P.Tufano1, S.Michelli1, Johns Hopkins School of Medicine, Baltimore, MD**

**Objective:** To determine the patterns of cervical LN disease recurrence in the lateral and central neck in patients with recurrent/persistent papillary thyroid cancer undergoing reoperative surgery. 

**Study Design:** Retrospective chart review. 

**Methods:** We reviewed the charts of 45 consecutive patients (February 2002-November 2007) with PTC who underwent first time reoperative surgery by the senior author (R.P.T.) for recurrent/persistent PTC. PTC were confirmed in either the lateral neck and/or central neck by ultrasound guided FNA biopsy. Reports of pre-operative FNA cytologic findings, the extent of lateral neck dissections by levels as well as central neck dissection, and post-operative final histopathologic examination were reviewed. 

**Results:** 45 patients underwent lateral neck dissection for recurrent/persistent PTC. 16 patients had previous attempts at lateral neck dissection at or after the time of the primary thyroid surgery with...
To investigate the safety and efficacy of the no-tie technique this is a multicenter, single-blinded, randomized clinical trial, Well differentiated thyroid cancer (WDTC) shows relatively. We will analyze the results of 98 patients included. These are undergoing reoperative thyroid surgery for nodal disease in the central neck are very likely to harbor concomitant gross nodal disease in the lateral neck. We encourage a level 2-5 lateral neck dissection or removal of all previously undissected levels when possible for this patient population.

**S012: SURGICAL MANAGEMENT OF TRACHEAL INVASION BY WELL DIFFERENTIATED THYROID CANCER**

**K.Lee**, Y.Lee, J.Jeong, S.Choi, C.Park, Hanyang University Hospital, Seoul Republic of Korea

**Objectives:** Well differentiated thyroid cancer (WDTC) shows relatively good prognosis but 10 to 15 percent of cases shows local invasion. Complete resection of locally invasive thyroid cancer may ensure a lower recurrence rate and better overall survival. However, in the cases of thyroid cancer with tracheal invasion, there is still debate in the extent of resection [shave excision and complete excision]. The purpose of this study is to determine the optimal management of tracheal invasion by WDTC.

**Method:** From 1996 to February 2005, 348 patients with WDTC (318 cases of papillary carcinoma and 30 cases of follicular carcinoma) were admitted for thyroidectomy. Of these, 23 patients had tracheal invasion. The medical records of 23 patients with tracheal invasion were reviewed retrospectively to analyze the grade of tracheal invasion, the methods of operations, recurrence and survival rates. The mean age of tracheal invasion group was 55.7 and male to female ratio was 1:1.2. The mean follow up period was 48 months (86±142). **Results:** In 6.6% (23 of 348) of WDTC patients, tracheal invasion was noted. Of 23 patients with tracheal invasion, 22 cases were papillary carcinoma and 1 case was follicular carcinoma. 19 patients underwent shave excision and 4 patients underwent complete surgical excision of tracheal invasion. In 26% (6 of 23) of tracheal invasion patients, recurrence was noted after surgery. Among 6 of recurred patients, local recurrence was 313%, regional recurrence was 417.4% and distant metastasis was 1 case. All of 6 cases with recurrence underwent shave excision and there was no recurrence in 4 patients with complete excision. Patients with tracheal invasion showed a lower 10 years survival rate compared to non-tracheal invasion patients (54.7 vs 99.0 percent, p=0.00). **Conclusion:** Based on the result of this study, it is suggested that the complete surgical excision might minimize the recurrence rate in patients with tracheal invasion by WDTC.

**S013: THE NO-TIE TECHNIQUE USING THE HARMONIC SCALPEL IN TOTAL THYROIDECTOMY WITH CND; A PROSPECTIVE RANDOMIZED STUDY**

Y.Koh, S.Lee, E.Choi, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea; Yonsei University College of Medicine, Seoul, Republic of Korea

**Objective:** To investigate the safety and efficacy of the no-tie technique using the harmonic scalpel (HS) in terms of the operating time and complications in total thyroidectomy with central neck dissection (CND). Recently, the HS has been used as an alternative to conventional hand-tied ligation for hemostasis in thyroid surgery, which is a time-consuming procedure. Very limited data have been published on evidence of its safety in total thyroidectomy. The aim of this study is to compare the outcomes of HS versus conventional hemostasis in total thyroidectomy.

**Methods:** Sixty-five consecutive thyroidectomized patients were enrolled in this study. The final pathology in all the patients was thyroid papillary carcinoma. All patients underwent total thyroidectomy with CND. The no-tie technique using HS group consisted of 31 patients. The conventional hand-tied ligation technique group comprised 34 patients. The following variables were examined: operating time, intraoperative bleeding, incidence of complications (laryngeal nerve palsy, hypoparathyroidism, temporary recurrent laryngeal nerve palsy, hypoparathyroidism, and injury to the adjacent structures including the trachea and esophagus), the number of pathologically proven lymph nodes, total amount of drainage, duration of drain placement, and time of hospital discharge. **Results:** The use of the HS reduced the operating time of total thyroidectomy with CND by a average of 43.12 min (p<0.001). The number of pathologically proven lymph nodes was 7.32 ± 1.66 in the NT group and 6.85 ± 1.76 in the CT group (p = 0.274). No significant difference was observed in the overall perioperative complications, such as postoperative bleeding, temporary recurrent laryngeal, nerve palsy, and temporary hypoparathyroidism, between the two groups. No permanent recurrent laryngeal nerve palsy and hypoparathyroidism occurred in either group. **Conclusions:** The no-tie technique with the HS is a relatively safe and effective method in total thyroidectomy combined with CND. Moreover, the HS significantly reduced the operating time.

**S014: MULTICENTER RANDOMIZED TRIAL ON HARMONIC SCALPEL VS. CONVENTIONAL HEMOSTASIS IN TOTAL THYROIDECTOMY: PRELIMINARY RESULTS**

A.L.Carvalho, A.Sanabria, L.P.Kowalski, on behalf of the BHNCSCG, Hospital de Cancer of Barretos, Barretos, Brazil; Universidade de La Sabana, Bogota, Colombia; Hospital ACCoargo, Sao Paulo, Brazil; Brazilian Head and Neck Cancer Study Group, Brazil

The use of Harmonic Scalpel in head and neck surgery is increasing in popularity. However, the cost-effectiveness of this new technology is still to be defined. **Objective:** The aim of this study is to compare the operating time, postoperative complications and outcomes in total thyroidectomy when using the Harmonic Scalpel (HS) versus conventional hemostasis (CH).

**Methods:** This is a multicenter, single-blinded, randomized clinical trial, involving 11 Brazilian Institutions. Inclusion criteria were: patients older than 18 years, no previous surgery in the neck and should undergo total thyroidectomy. If thyroid cancer diagnosis, should have no indication for lateral or radical neck dissection nor proved local invasion. Protocol was approved by the IRB in each institution and all patients signed the informed consent previously to its participation on the study. The main outcomes were: postoperative pain, drainage volume, hypocalcemia, nerve palsy, and operative time.

**Results:** We will analyze the results of 98 patients included in the study so far: Fifty-two patients underwent total thyroidectomy in the HS group and 46 were allocated to the CH group. We found significant differences between the HS and CH groups at baseline. Postoperative pain, drainage volume, hypocalcemia and nerve palsy was similar in both groups. The only significant difference between the groups was the operative time: we observed a shorter operative time in the HS group compared to the CH group (p=0.01).

**Conclusions:** Our preliminary results did not show differences in postoperative pain, drainage volume, and transient hypocalcemia or nerve palsy in patients undergoing total thyroidectomy regardless of the patients’ group allocation. We did confirm that the use of the HS may significantly reduce operative time in total thyroidectomy compared to the CH.


**S015: A COMPARISON OF OUTCOMES IN MINIMALLY INVASIVE VIDEO-ASSISTED THYROIDECTOMY VS. OPEN THYROIDECTOMY**

A.S.Ketcham, J.D.Horning, E.J.Hentsch, F.S.Lee, M.B.Gillespie, K.G.Hoang, J.D.Osguthorpe, J.Fernandes, M.S.Richardson, T.A.Day, 1Medical University of South Carolina, Charleston, SC

**Objective:** Although minimally invasive video-assisted thyroidectomy (MIVAT) remains controversial, its use internationally continues to increase. We compare open thyroidectomy (OT) vs. MIVAT from an American perspective and specifically emphasize practicality, safety, cost, and patient satisfaction. **Methods:** Patients meeting the criteria for MIVAT were selected through a retrospective review over 22 months and were classified into two cohorts: open thyroidectomy (OT), including both conventional and minimally invasive, and MIVAT. Inclusion criteria for MIVAT were thyroid nodules < 27 cc, of previous ipsilateral thyroid surgeries, and absence of thyroiditis, metastatic disease, or significant substernal or retroesophageal extension. Cohort characteristics were analyzed. Surgical outcome was compared using operative time, blood loss, complications, length of hospital.
S016: MANAGEMENT OF RECURRENT LARYNGEAL NERVE INVASION BY LOCALLY INVASIVE WELL DIFFERENTIATED THYROID CANCER

K. Tae1, Y. Lee1, Y. Lee1, R. Ryu1, K. Kim1, 1Hanyang University Hospital, Seoul, Republic of Korea

Objective: The incidence of recurrent laryngeal nerve (RLN) invasion by thyroid cancer ranges from 2.8% to 19.4%. Differing philosophies exist for the optimal management of RLN invasion by well-differentiated thyroid cancer (WDTC). Method: A retrospective study was performed with the medical records of 29 patients with RLN invasion among 330 patients with WDTC between 1996 and 2005. Clinical variables such as preoperative vocal cord mobility, the status of nerve invasion, recurrence, pathology, treatment and postoperative vocal cord function were analyzed. All of 29 patients with RLN invasion underwent total thyroidectomy and postoperative radioactive iodine ablation. Results: In 8.7% (29 of 330) of WDTC patients, RLN was involved. Of 29 patients with RLN invasion, 10 had vocal cord paralysis and 19 had normal vocal cord function preoperatively. RLN was involved unilaterally in 26 patients and bilaterally in 3 patients. In all of 10 patients with vocal cord paralysis preoperatively, RLN was sacrificed. Of 19 patients with mobile vocal cord preoperatively, 13 cases received shaving off procedure to preserve RLN and 6 cases with direct invasion. Only 1 patient with shave off RLN received sacrifice of RLN. Of 3 patients with bilateral RLN invasion, one side RLN was sacrificed and the other side RLN was shaved off and preserved. Of 14 RLN of shaving off procedure, 1 showed permanent vocal cord paralysis, 4 showed transient paralysis and 9 showed normal vocal cord function. Local recurrence rate was not statistically related between RLN resection group and preservation group (p=0.356). Conclusion: If RLN is paralyzed preoperatively, it needs to be sacrificed. If RLN is functioning preoperatively and no direct invasion, however, the RLN can be preserved with shaving off procedure without leaving gross tumor behind. Patients with residual microscopic disease should have postoperative radioactive iodine ablation.

S017: RECURRENT LARYNGEAL NERVE PALSY AFTER THYROIDECTOMY. A SYSTEMATIC REVIEW

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Objectives: Recurrent Laryngeal Nerve Palsy (RLNP) is a recognized possible complication after thyroid surgery. It may present with various of symptoms, such as voice change and respiratory symptoms. However, it may remain undetected and the true prevalence may be under-reported. The aim of this study is to determine the prevalence of temporal and permanent palsy after thyroid surgery. Methods: A Medline search was performed. A Meta analysis was undertaken which included 27 articles and 25,000 patients. Confidence intervals were calculated and Forest plots produced. Results: Three methods of diagnosing RLNP were used: indirect laryngoscopy, flexible laryngoscopy and video-stroboscopy each method had different reported rates of RLNP. The mean prevalence of temporal RLNP after thyroid operations was 9.95% and the prevalence of permanent RLNP 2.38%. The RLNP rate varied according to the method of examining the larynx and ranged from 26% to 2.3%. Most of the reviewed studies recommend a follow up period up to one year to assess and evaluate RLNP. Conclusion: Our study has identified a wide disparity in reported RLNP rates. We propose fibre-optic laryngoscopy to become the gold standard for assessing the voice after thyroidectomy in order to reduce bias.

HUMAN PAPILLOMAVIRUS

S019: PREVALENCE, MORPHOLOGY AND PROGNOSIS OF HUMAN PAPILLOMAVIRUS IN TONSILLAR CANCER

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Objective: Recent data from the Surveillance, Epidemiology and End Results (SEER) program has demonstrated an increase in the incidence of tonsillar carcinoma by 16% from 1973-2002 which leads all other head and neck cancer sites. The association of HPV (human papillomavirus) with head and neck cancer has been established, but many studies do not associate HPV with a specific cancer site. The goal of this study was to identify the prevalence of HPV in tonsillar squamous cell carcinoma (SCC), as well as the relationship of HPV to prognosis and tumor morphology. Methods: This study consisted of a retrospective analysis of primary tonsillar carcino-
ma treated at our institution from 1989-2006. In situ hybridization was performed on all archived tonsillar tissue with a probe labeling for HPV 16, 18, 31, 33. Tissue was evaluated for integration of the virus based on staining pattern. Adjacent tissue sections were stained with hematoxylin and eosin. These were reviewed to identify morphological characteristics. Patients undergoing tonsillectomy for chronic tonsillar folliculitis (CTF) were used as age and gender matched control subjects. Data was also retrieved on patient demographics, risk factors, treatment, and outcomes. Results: Of the 48 patients with tonsillar carcinoma, in situ hybridization identified 35% as HPV positive tumors, whereas the remaining 65% were HPV negative. Age matched controls had no evidence of HPV. There was no significant difference between HPV positive and negative patients regarding age (P=0.336), smoking Hx (P=0.591), EOH Hx (P=0.91), and treatment (P=0.51). Utilizing a minimum of 36 months follow-up, 31 of the 48 total subjects were eligible for outcome analysis. The overall rate of recurrence in this population was 37%. There was no significant difference in either the incidence of recurrence (P = 0.258) or disease specific survival (P = 0.4) between the HPV positive and HPV negative groups. 25% of the patients from 1989-1999 had HPV positive tumors, whereas 48% from 2000-2007 demonstrated tumors associated with HPV. We observed a significant difference in clinical outcomes based on viral status. The occurrence of HPV associated tonsillar cancer has clearly risen recently. We observed that HPV positive tumors had their origin in the tonsillar crypts, whereas non-HPV associated tumors more often arose from the surface epithelium. Future investigation of the immunological properties of HPV associated SCC could provide insight in developing targeted therapies for this specific patient population.

SO20: A COMPARATIVE ANALYSIS OF HUMAN PAPILLOMAVIRUS INFECTION IN TONSILLAR, GLOTTIC AND TONGUE CANCERS S.Lee1, N.Cho2, E.Choi2, S.Kim2, 1College of Medicine, Chung-Ang University, Seoul, Republic of Korea, 2Yonsei University College of Medicine, Seoul, Republic of Korea

Objective: Human papillomavirus (HPV) infection is controversial as a causative factor in head and neck cancers despite the relatively high frequency of HPV infection in extragenital organ cancers. We aimed to examine the prevalence and physical status of HPV in 182 cases of head and neck cancers. Methods: In order to clarify whether HPV directly affects the carcinogenic potential of this virus. This study found that 35% of tonsillar carcinoma at our institution was associated with HPV, but failed to demonstrate a difference in clinical outcomes based on viral status. The occurrence of HPV associated tonsillar cancer has clearly risen recently. We observed that HPV positive tumors had their origin in the tonsillar crypts, whereas non-HPV associated tumors more often arose from the surface epithelium. Future investigation of the immunological properties of HPV associated SCC could provide insight in developing targeted therapies for this specific patient population.

SO21: CHRONIC PERIODONTITIS, SMOKING AND HUMAN PAPILLOMAVIRUS 16 INTERACTION IN BASE OF TONGUE CANCERS C.A. Treadwell1, M.A. Sullivan2, D.L. Stoler1, T.Loree2, D. Hyland2, P.J. Smaldino2, N. Rigual2, T. Loree2, 1State University of New York at Buffalo, Buffalo, NY, 2Roswell Park Cancer Institute, Buffalo, NY

Objective: Substantial evidence has accumulated for high risk human papillomaviruses (HPV) in oropharyngeal cancers. However, most HPV infections are transient and do not cause malignancy indicating that cofactors are critical for progression to cancer. Co-infections in the cervical with particular bacteria, such as Chlamydia trachomatis and overt cervicitis were shown to act synergistically with HPV to increase cervical cancer risk. Periodontitis is a chronic oral infection and may be a key player for the acquisition and persistence of oral HPV. The association between smoking and HPV prevalence in the literature is inconsistent. Smoking has been associated with both HPV- and HPV+ cancers although recent studies have shown that HPV-positive cancers are more likely to occur in never-smokers. Our objective was to assess the independent and joint effects of chronic periodontitis and smoking on tumor HPV status in base of tongue cancers. Methods: We performed a case-control study using existing data at Roswell Park Cancer Institute, Buffalo, NY. The study population consisted of all patients diagnosed with primary base of tongue squamous cell carcinoma between 1995 and 2007 who had data on both periodontitis and tumor HPV status (N=27). Cigarette, pipe, or cigar smoking status was defined as never and ever. Cumulative history of periodontitis was assessed by alveolar bone loss (ABL) in millimeters (mm) from panoramic radiographs. Periodontitis was defined as ABL 2652.75 mm. Tumor HPV-16 DNA status was identified by polymerase chain reaction. 2-sided Fisher019s Exact was used to test the associations. Results: The prevalence of smoking (81.5%), periodontitis (66.7%) and HPV-16 DNA (66.7%) were all high. History of periodontitis was strongly associated with tumor HPV status regardless of smoking status (p=0.001). 88.9% of subjects with periodontitis and only 22.2% of those without periodontitis had HPV+ tumors. On the other hand, smoking status was not a good predictor of the tumor HPV status (p=0.808). All nonsmokers had HPV+ tumors. However, more than half (59.1%) of the smokers also had HPV+ tumors. Stratification by periodontitis revealed that all never smokers with HPV+ tumors had periodontitis (table 1). Among smokers, 84.6% of those with periodontitis and only 22.2% of those without periodontitis had HPV+ tumors. Conclusions: Our results suggest an interaction between chronic periodontitis and smoking for tumor HPV status in base of tongue cancer. Identifying the relationship between the virus, smoking and the effects of other host and environmental influences may be essential for gaining insight into the biology of HPV-associated carcinogenesis.


Introduction: In the United States, oropharyngeal (OP) squamous cell carcinoma (SCCa) is associated with oncogenic human papilloma viruses (HPV) in as many as 70% of the cases. In addition, this type of OP SCCa has increased in incidence in recent decades. Since it is reasonable to assume that HPV-induced oncogenesis is preceded by infection of the OP with oncogenic HPV [much like in the uterine cervix], an understanding of the prevalence of HPV infection in OP is in the general population is desirable. This would help define the size of the at-risk population and help determine the transformation rate from infection to carcinoma. Methods: We used archived, non-embedded non-cancerous palatine tonsils from patients aged 21 to 70 years from two different time periods, 1979 to 1983 (Group A) and 1999 to 2003 (Group B), all from a single institution in El Paso County, Colorado. Seventy-six specimens were in Group A and 84 were in Group B. These were aged and gender matched. All specimens were analyzed with HPV 16 and 18 type-specific DNA-polymerase chain reaction (PCR) primers after DNA extraction. Our hypothesis was that the prevalence rate would be higher in the more recent group (Group B), commensurate with the rise in incidence of HPV-positive OP SCCa. Results: All specimens in both groups were negative for HPV 16 and 18. Thus, the prevalence of HPV infection in the palatine tonsils in the general population age 21 to 70 was <1.2% in Group A and <1.3% in Group B. Conclusion: This analysis shows a low prevalence of HPV infection in the palatine tonsils in the general population in a single county in Colorado known to have a rising rate of HPV-positive OP SCCa. Analysis of oropharyngeal tissues from individuals at highest risk of developing HPV-positive OP SCCa (middle-aged males) is likely to provide a higher prevalence rate.

SO23: HUMAN PAPILLOMAVIRUS AND TOBACCO USE IN BASE OF TONGUE CANCERS P.J. Smaldino1, D.L. Stoler1, M.A. Sullivan1, N.R. Rigual1, S.R. Popat1, W.L. Hicks, Jr.1, M. Merzianu2, D.P. Gaile1, G.R. Anderson1, T.R. Loree2, 1Roswell Park Cancer Institute, Buffalo, NY

Objective: Human Papillomavirus HPV and tobacco use are both associated with human oropharyngeal cancers, where they strongly appear to be playing causative roles. Successful public health efforts to reduce tobacco use have resulted in an overall reduction in head and neck cancers at all sites except the oropharynx, suggesting an increasing role for HPV, particularly HPV-16, in the etiology of this disease. The objective of this study was...
to examine the role of HPV and tobacco use in tongue base cancers. **Methods:** Base of tongue tumor DNAs from 30 Roswell Park Cancer Institute patients who had a pathological diagnosis of squamous cell carcinoma between 1995 and 2007 were subjected to PCR type specific analyses for HPV-16 and HPV-18. Primers specific for the HPV E6 transforming gene for each virus type were utilized to determine the incidence of the virus in these tumors. Demographic and clinicopathologic data including patient age, gender, race, tumor stage, differentiation and survival were obtained from each patient's medical record. **Results:** For HPV-16, amplification of the 109 bp fragment, diagnostic for the HPV E6 gene, was observed in 20 of 30 (66.6%) tumors. None of the tumors were positive for HPV-18. The use of tobacco was the only clinical, pathological or demographic feature found to be significantly associated with HPV status. Amongst the 26 men and 4 women in this study, 15 patients were smokers/tobacco users, 8 were former users and 6 had never used tobacco products. Tumors from 100% (6/6) of patients that had never smoked tested positive for the presence of HPV, compared to 57% (13/23) of those who had ever used cigarettes or tobacco products. No tumors were found that were not associated with either tobacco or HPV. These results were significant when analyzed by Fisher's Exact Test (p=0.042). When the proportion of HPV positive tumors from never smokers combined with former smokers [minimum of 6 years post smoking cessation] was compared with that of current smokers the difference was also highly significant (p=0.025). No significant associations were found when looking at sex, race, age at diagnosis, stage, patient status or degree of tumor differentiation with respect to HPV status. **Conclusions:** Some base of tongue tumors are associated with HPV, some are not. The association appears that none are associated with neither. This is consistent with the hypothesis that either tobacco or HPV are necessary in the etiology of these tumors. These data could suggest that this particular tumor may be prevented with vaccination for HPV, combined with anti-tobacco efforts.

**SO24: EFFECT OF HPV ON TREATMENT OUTCOME AND SURVIVAL IN OROPHARYNGEAL CARCINOMA ANALYSIS OF THE RANDOMIZED DAHANCA 5 & 7 TRIALS**

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**Objective(s):** To demonstrate the correlation between p16 overexpression and Human Papilloma Virus (HPV) infection in oropharyngeal squamous cell carcinoma and to examine the prognostic impact of p16 status in a prospectively analyzed cohort of Danish oropharyngeal cancer patients enrolled in the randomized DAHANCA 5 & 7 trials. **Methods:** A Tissue Micro Array (TMA) consisting of 32 tonsillar carcinomas was constructed and detection of HPV-DNA type 16 was done by situ hybridization. The TMA was evaluated by immunohistochemistry for p16 overexpression. Tumors were classified as: HPV16 positive, HPV16 negative. Between January 1986 and December 1999 The Danish Head and Neck Cancer group DAHANCA conducted the nationwide DAHANCA 5, 6&7 randomized trials, focusing on overcoming the disadvantages of tumour cell hypoxia and accelerated tumour cell proliferation. Overgaard J. et al. Radiother. Oncol. 46 (1998):135-146; Lancet 362 (2003): 933-940.) In the present study 335 pre-treatment oropharyngeal tumor blocks from patients enrolled in these trials were evaluated by immunohistochemistry for p16 status as described for the TMA-study. **Results:** 20 of 32 (62.5%) tonsillar carcinomas were HPV 16 positive and 19 of these were p16 positive corresponding to a sensitivity of 0.95. 12 tumors were HPV 16 negative and 10 of these were p16 negative corresponding to a specificity of 0.83. The two markers matched in 29 of 32 (90%) of the tumours. Based on this we concluded that p16 is a reliable indicator of HPV infection in oropharyngeal squamous cell carcinomas and decided to use p16 as an indicator of HPV infection. In total 135 of the 335 oropharyngeal tumours were p16 positive corresponding to 40%. We observed no statistical significant differences between the p16 positive and p16 negative groups regarding tumour stage, gender and age. In univariate analysis, loco-regional tumour control was significantly improved for p16 positive patients with 5-year actuarial values of 67% versus 36% for p16 negative tumours, p < 0.0001. A similar beneficial outcome for p16 positive tumours was observed for the 5-year actuarial values for cancer specific survival (69% versus 35%, p< 0.0001) and overall survival (54% versus 18%, p< 0.0001). In a Cox proportional hazard multivariate analysis p16 overexpression remained a very strong independent predictor for loco-regional tumour control (HR: 0.27 [0.14 - 0.52], p< 0.0001). From a Cox proportional hazard multivariate analysis p16 overexpression remained a very strong independent predictor for cancer specific survival (HR: 0.27 [0.14 - 0.52], p< 0.0001) and overall survival (OR: 0.33 [0.24 - 0.46]) respectively. p16 was an even stronger prognostic factor related to these outcomes than the clinical parameters T-stage and Nodal-status. **Conclusions:** p16 overexpression proved to be the strongest independent prognostic factor related to survival and loco-regional tumour control in our study and so we conclude that HPV infection is significantly correlated to improved prognosis and response to radiotherapy in oropharyngeal cancer patients treated with this modality. Presented on behalf of the Danish Head and Neck Cancer group (DAHANCA).

**SO25: POSSIBLE VIRAL ETIOLOGY FOR ORAL TONGUE CANCERS IN PATIENTS WITH NON DRINKING/SMOKING ETIOLOGY AND NO HPV SEQUENCES**

**E.M.Zafereo** 1, **G.Li** 2, **C.A.Viamonte** 1, **A.K.El-Naggar** 2, **M.D.Williams** 2, **C.Zhao** 2, **Q.Wei** 2, **E.M.Surgi** 2, 1, **Baylor College of Medicine, Houston, TX; 2MD Anderson Cancer Center, Houston, TX

**Objective:** There has been an increase in the incidence of tongue cancer, especially in a much younger population who have not been exposed to the traditional risk factors of cigarette smoking and alcohol use. We first analyzed 51 oral tongue cancers and 65 base of tongue/tonsillar cancers for the presence of HPV16. We utilized real-time specific PCR analysis, as well as HPV universal primers searching for the presence of HPV sequences in these cancers. We found only one oral tongue cancer with HPV sequences while 45% of the base of tongue/tonsillar cancers contained HPV16 sequences. Thus, what is the cause of the oral tongue cancers in the younger individuals without a drinking or smoking history? In an attempt to answer this question we performed gene expression profiling on six oral tongue cancers from patients with a drinking and smoking history and six younger patients without this history. We found a number of genes with profound expression differences between these two groups. One very interesting gene which was expressed at much higher levels in the tumors from the patients without a drinking or smoking history was KRT14. This gene was previously shown to have increases in expression in response to the presence of HPV-specific gene expression. We undertook a study of HPV16 in oral cavity cancers to explore a possible association between HPV16 and oral cavity cancers occurring in young patients.

**Methods:** We identified 136 newly diagnosed, previously untreated oral cavity cancer patients (39 patients under 40 years of age, and 63 patients under 50 years of age) presenting to a large multidisciplinary center. As expected, patients under the age of 40 were more commonly female, never-smokers, and never-drinkers with oral tongue cancer. Among patients under 40, 16 of 39 (41.0%) tumors were both HPV16 E6 and E7 positive corresponding to 40%. We observed no statistical significant differences between these two groups. One very interesting gene which was expressed at much higher levels in the tumors from the patients without a drinking or smoking history was KRT14. This gene was previously shown to have increases in expression in response to the presence of HPV-specific gene expression. We undertook a study of HPV16 in oral cavity cancers to explore a possible association between HPV16 and oral cavity cancers occurring in young patients.

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patients who had both HPV16 E6 and E7 positive specimens was 40.6 years (median 39 years), while the mean age at presentation of patients who did not have both HPV16 E6 and E7 positive tumors was 54.3 years (median 53.5 years) (P<0.001). The mean age at presentation of patients who had either HPV16 E6 or E7 positive tumors was 43.8 years (median 40 years), while the mean age at presentation of patients who had both HPV16 E6 and E7 negative specimens was 54.7 (median 53.5 years) (P=0.0003). Patients in their 40’s had an intermediate prevalence of HPV16, with 25.0% positive for both HPV16 E6 and E7 and 33.3% positive for either HPV16 E6 or E7. The trend for increasing prevalence of both HPV16 E6 and E7 positivity correlated significantly with decreasing age (P<0.01). Conclusion: While HPV16 does not appear to be important to the etiology of the majority of oral cavity cancers, a significant attributable fraction of oral cavity cancers in young adults may be associated with HPV16.

S027: RADIATION THERAPY INDUCES AN IMMUNOLOGIC CLEARANCE OF HPV POSITIVE HNSCC IN MICE W.C..Spano1, D.W.Lee1, M.E.Anderson1, A.Hoover1, J.H.Lee2, 1University of Iowa, Iowa City, IA; 2University of Iowa, Iowa City

Objectives: Human papilloma virus causes up to 40% of HNSCC. Although HPV positive tumors present at an advanced stage, multiple studies have shown a survival advantage compared to HPV- HNSCC when treated with external beam radiation. In these studies we have correlated radiation sensitivity both in vitro and in vivo to HPV status in human cancer cell lines, transformed primary human tonsil epithelial cells, and transformed primary mouse tonsil epithelial cells. Using an HPV+ and HPV- syngeneic mouse model we also show that this clearance in vivo requires an active immune response. Methods: To determine cellular sensitivity to radiation we have completed in vitro clonogenic survival assays following escalating radiation doses on the different cell types listed in the objective. We have created a syngeneic mouse model of HPV+ and HPV- HNSCC by transforming mouse primary tonsil epithelial cells with either HPV16 oncoproteins or non-oncogenic RNAi strategy that affects similar oncogenic pathways. Using these transformed cells we examined the radiation treatment of HPV+ and HPV- tumors in immune competent and immune incompetent mice. Results: The in vitro clonogenic survival assays demonstrate that HPV +/- cells are more resistant to radiation therapy compared to their HPV-counterparts. This result was consistent for human cancer cell lines, HPV transformed primary tonsil keratinocytes, and HPV transformed mouse primary tonsil keratinocytes. In contrast, increased tumor clearance was observed in HPV positive tumors after radiation therapy in vivo. HPV tumors were much more sensitive in vivo and at 20 gray of radiation HPV+ tumors were eradicated compared to the HPV- counterpart that showed persistent growth. To understand whether an immune response could explain this enhanced eradication, we completed identical studies in mice lacking an ability to mount a specific cell response. HPV positive tumors in these syngeneic immune incompetent mice mimic the in vitro results by showing an increased resistance to radiation. Conclusions: HPV positive tumors are not more curable based on an increased native sensitivity to radiation therapy. Our results support the hypothesis that radiation therapy induces a tumor clearing immune response to this antigenic cancer. The implications from these results may lead to novel therapies that enhance tumor eradication for HPV+ cancers.

OUTCOMES: QUALITY OF LIFE

S028: PRE-TREATMENT CLINICAL FACTORS PREDICT RESPONSE TO TREATMENT (IN REGARDS TO POST-TRIAL QUALITY OF LIFE M.W.El-Deir1, J.E.Weymuller2, N.D.Futran3, J.McDowell4, B.Yueh5, 1University of South Florida, Tampa, FL; 2University of Washington, Seattle, WA; 3Puget Sound VA Research Group, Seattle, WA; 4University of Minnesota, Minneapolis, MN

Objective: Emerging evidence in survivorship research suggests that long-term quality of life may be as strongly predicted by pre-treatment factors as by treatment modality. In addition, ancillary treatment may also strongly influence quality of life. The purpose of this study is to report on predictors of long-term quality of life in a large cohort of H&N cancer patients. Methods: Quality of life data on over 500 patients were available. After including only patients with squamous cell tumors of the oral cavity, oropharynx, hypopharynx, and larynx, and only patients with full functional and diagnostic quality of life data on at least two occasions over a 2-year period, the resulting analyzable dataset included 177 patients. The database and medical records were used to capture data on demographic variables, co-morbidities, TNM stage, tumor site, pre-treatment quality of life (UW-QOL), treatment, gastrostomy and tracheotomy status, disease status and quality of life at one year. Bivariate analyses were used to test hypothesized relationships, and multivariate regression analyses were used to identify independent predictors of long-term quality of life. Results: The strongest bivariate relationships were observed between long-term UW-QOL scores and pre-treatment UW-QOL scores (r=−.58, P<.0001). Strong relationships were also found with acute complications (ACE-27, r=.001). T-stage and N-stage strongly influenced long-term UW-QOL scores as has been previously demonstrated. Post-treatment influences included disease status, tracheotomy status, and gastrostomy status. Patients with gastrostomies had UW-QOL scores 11.5 points (P<.001) worse than those without; a 7 point difference is considered clinically significant. This observation should be compared with the finding that patients with recurrent or persistent disease had UW-QOL scores only 7.5 points worse than those without disease. Demographic, tumor site, and treatment modality had little predictive value for long-term UW-QOL scores. In multivariate regression models, pre-treatment quality of life scores and co-morbidity had the strongest predictive value on one-year UW-QOL scores. Conclusions: Our findings support the notion that pre-treatment function and co-morbidity have strong influences on not just survival, but also quality of life. The strong correlation between pre- and post-treatment quality of life suggests that pre-treatment function is important to measure, since it has stronger influence on quality of life than the type of treatment that is offered. We also found it of note that the presence of a PEG tube had a stronger influence on quality of life than the presence of disease, suggesting that swallowing function is critically important to maintaining good quality of life after therapy.

S029: LONG-TERM ACCEPTANCE OF MAJOR SURGERIES AND QUALITY OF LIFE OF ADVANCED HEAD AND NECK CANCER SURVIVORS J.G.Vartanian1, I.P.Kowalski2, I.A. Camargo Hospital, Sao Paulo, Brazil

Objective: Considering the treatment outcomes of head and neck neoplasms, major surgical procedures, with or without adjuvant radiotherapy, are credited to be the most aggressive treatment modality regarding functional outcomes. The purpose of this study was to evaluate the acceptance of the surgical treatment and the quality of life of long-term survivors of advanced head and neck cancer at a single institution. Methods: This is a cross-sectional study of a consecutive series of patients treated for advanced primary squamous cell carcinoma of the upper aerodigestive tract cancer. All patients were submitted to surgery, with or without radiotherapy, with a minimum disease-free survival period of 2 years. All medical charts were reviewed for demographic and clinical data. The patients completed a Portuguese version of the UW-QOL, and a specific questionnaire about their acceptance of long-term outcomes. Results: A total of 273 patients were studied, most male (74.4%), with a median age of 56 years. The tumor site was oral cavity in 101 cases, oropharynx in 64 (23.4%), larynx in 91 (33.3%) and hypopharynx in 17 (6.2%). There were 167 (61.2%) of T3 and 106 (38.8%) of T4 tumors. Radiotherapy was performed in 153 patients (56%). The global quality of life was considered good to excellent by 162 patients (60%), with a mean UW-QOL composite score of 79.3. Seventy-four percent of patients reported that their health status was the same or better than their status before treatment. The composite score of the UW-QOL was worse in patients with oropharynx and hypopharynx tumors, as well as in patients with T4 tumors. The majority of patients (91.2%) reported that they would undergo the same treatment again. 95.6% of patients reported that they would not like to change the present outcome for another treatment option with a lower chance of cure but with an improved quality of life. Conclusion: Previous reports have addressed that a considerably number of patients with advanced head and neck tumors who underwent surgical treatment were unsatisfied with treatment outcomes, with a poor quality of life. Also, other studies reported that some healthy individuals would prioritize the quality of survival instead of quantity of life. In this series, the vast majority of patients considered the radical surgery the best option of treatment and reported a good and acceptable quality of life.
Objective: To determine whether the Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire is a sensitive, reliable and valid measure of shoulder disability in patients who have undergone a neck dissection.

Methods: A cross-sectional mail out study was undertaken, with the exception of a second mailing for test-retest reliability. Known group validity was assessed by evaluating differences in DASH scores between patients undergoing different types of neck dissections, where score differences in shoulder dysfunction were expected based on the type of neck dissection performed. Construct validity was assessed by correlating DASH scores with the Neck Dissection Impairment Index (NDII) scores, a validated outcome measure previously used in this patient population. A sensitivity questionnaire was completed by both patients and head and neck surgeons. 153 eligible patients were sent questionnaire packages via the mail using a modified Dillman approach, with a response rate of 80% (109/137) and 53% (50/94), respectively. All patients were greater than 11 months from their surgery with a median time of 31 months.

Results: The DASH questionnaire was completed by 111 patients (80% response rate). It demonstrated good internal consistency with Cronbach’s α = 0.82. The modified DASH had better sensitivity than the NDII (p = 0.0005). There were significant differences between treatment groups (p < 0.05) with modified radical neck dissection patients having greater shoulder disability than both modified radical neck dissection (p = 0.029) and selective neck dissection patients (p = 0.007). However, while modified radical neck dissection patients had higher disability scores than selective neck dissection patients the difference was not statistically significant (p = 0.017). Similar differences were noted with the NDII. The Pearson correlation coefficient between the DASH and NDII was 0.916. Based on a priori criteria the DASH was judged to be sensitive by both patients and head and neck surgeons.

Conclusion: The DASH is a sensitive, valid and reliable instrument for assessing shoulder disability following neck dissection. However, the increased number of items contained in the DASH does not seem to increase the ability to detect differences in shoulder disability between patients when compared with the NDII.

S031: SWALLOWING QUALITY OF LIFE IN ADVANCED LARYNX AND HYPOPHARYNX CANCER TREATED WITH ORGAN PRESERVATION VS. SURGERY

Objective: Patients with advanced laryngeal cancer have similar survival rates, whether they are treated with surgery or chemoradiation therapy. However, organ preservation does not necessarily imply functional preservation. Swallowing is a major quality of life issue that has not been comprehensively studied in this population. The objective of this study is to compare swallowing QOL in patients treated with organ preservation or surgery. Different patient groups were compared including laryngeal and hypopharyngeal cancer.

Materials/Methods: It is a cohort study. All consecutive patients with stage III/IV larynx or hypopharynx cancer treated with surgery or organ preservation between 1999-2005 were identified from a single tertiary care centre. The primary outcome measure was the MD Anderson Dysphagia Inventory (MDADI). Secondary subjective outcome measures included the Head and Neck Quality of Life (HNQOL) for general QOL, and Patient Generated Subjective Global Assessment (PG-SGA) for nutrition. Secondary objective outcome measures included incidence and duration of tube feeding, esophageal strictures and dilatations. Outcomes were compared between treatment groups. Results: 120 patients were identified with 58 patients alive at time of analysis. 38 patients completed questionnaires. No statistical differences were found for overall subjective outcome measures between the treatment groups. However, multivariate analysis revealed swallowing QOL was worse in groups of multimodality treatment, advanced stage and hypopharyngeal subtype. Tube feeding rates were significantly higher with CRT (68.2%), compared to surgery and post-op RT (25%, p = 0.003), surgery alone (23.5%, p = 0.010), and RT alone (25.8%, p = 0.002). CRT was also associated with a 75% incidence of prolonged tube feeding requirement, compared with 0% in patients treated with surgery alone and RT alone. Conclusions: Organ preservation with CRT is associated with more frequent and prolonged use of nutritional support in the short term. In the long-term, subjective assessment of swallowing QOL is good, regardless of treatment modality.

S032: LONG-TERM HEALTH-RELATED QUALITY OF LIFE

Objective: As the number of cancer survivors in the U.S. continues to increase, the health issues confronting this group which includes head and neck cancer survivors, are emerging as a major public health concern. Substantial knowledge gaps exist regarding even the most fundamental of these issues in long-term survivors of head and neck cancer. This paper reports the health-related quality of life in 5 year survivors of head and neck cancer.

Methods: Prospective observational study of head and neck cancer survivors, more than 5 years out from diagnosis utilizing measures of general health and head and neck specific quality of life, depression, social support, and pain. Multivariate analysis of factors related to long-term health related quality of life results.

Results: Data are reported on 178 patients. Over a third of patients are in the lowest quartile for physical and mental functioning compared to age matched controls in the general population. Over 50% have a compromised ability to eat. 14% reported moderate or severe pain. 30% demonstrated some level of depressive symptomatology. 20% of patients continued to smoke and 40% reported use of alcohol. Advanced age was predictive of worse physical health and less depression. Advanced stage was predictive of poor oral functioning. Pain at long-term follow-up was an independent predictor of poor health related quality of life in all areas except aesthetics.

Conclusions: This study identified key health-related quality of life issues in long-term head and neck cancer survivors. This initial study will facilitate future studies and interventions.

S033: SCREENING FOR DYSFUNCTION TO PROMOTE MDT INTERVENTION USING THE UNIVERSITY OF WASHINGTON QUALITY OF LIFE QUESTIONNAIRE

Objective: Head and neck oncology patients can have significant dysfunction following diagnosis and treatment which can easily go unrecognized in busy outpatient clinics. It would be helpful to clinicians and multi-disciplinary teams if a short screening questionnaire could quickly identify patients with possible dysfunction requiring further evaluation and intervention. The University of Washington quality of life scale (UW-QOLv4) is a short multi-domain self-completed questionnaire already in common use with this population, the current version since 2000. The aim of this research was to investigate the potential of the UW-QOL as this quick screening tool and to see the effect of cut-off strategies at various times in the cancer journey and for different clinical subgroups.

Method: Several studies between 2000 and 2006 used the UW-QOL in parallel with detailed established questionnaires to identify one or more single item UW-QOL domains to be compared for agreement against relevant detailed questionnaires and allowed appropriate UW-QOL cut-offs for severity of dysfunction to be determined. The detailed questionnaires included EQ-5D, DAS 24, SWAL-QOL, MDADI, LORQ, VHL, VRQOL, NDI, SDI, EORTC H&N, QEGoLS, CES D and HAD. Studies recruited consecutive groups of disease-free patients. Four postal surveys recruited survivors with SCC oral or oro-pharyngeal disease after primary surgery with or without adjuvant radiotherapy. One clinic based study targeted speech and swallowing in survivors with SCC oropharynx and another targeted shoulder function in patients with various diagnoses. Another study recruited a non-cancer quota sample attending general dental practice.

Results: The results of these separate studies informed the cut-off strategies which were then applied to the Liverpool research database comprising 758 consecutive patients with SCC oral or oro-pharyngeal cancer having primary surgery with or without adjuvant radiotherapy during 1992-2005. From 2000 to May 2006, 79% (487) of the 613 survivors of this cohort completed one or more UW-QOLv4 questionnaires (median 3, 161.5 in all) the median time from surgery being 36 months, IQR 15-65 months. Analyses of these questionnaires enabled preliminary cut-off strategies to be developed for each domain that selected between 9% (recreation and speech) and 16% (swallowing) of questionnaires. Stratifying the results by different stages in the patient journey indicated that pain, mood and anxiety are particular concerns before operation whilst at 6 months swallowing, chewing, taste, saliva, mood and anxiety are dominant issues and that by 12 months and in the longer run there is a more even balance of concerns. A high percentage (81%) of patients had free-fall pain with adjuvant radiotherapy for T3/T4 tumours were triggered at around 2 years, with 42% triggered on 0 or more domains.

Conclusions: This study would suggest that the UW-QOLv4 can be used as a routine screening measure in clinical practice and a pragmatic cut-off for each domain is given.
SO34: CONTINUED ALCOHOL USE IN PATIENTS WITH HEAD AND NECK CANCER

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Objective: Although alcohol’s role in the development of squamous cell carcinoma of the head and neck is well established, it has been shown that a large proportion of this patient population is not aware of the association. This finding suggests that patients are not being given sufficient information about the detrimental effects of post-treatment alcohol use. The lack of appropriate counseling may be the result of conflicting information, such as a 2001 study which suggested that post-treatment alcohol consumption in moderation may be acceptable, despite its etiologic risk, due to alcohol’s apparent association with better health-related quality of life (QOL).

The purpose of the current study was to examine factors that predict continued alcohol use and the effect of such alcohol consumption on overall QOL one year after diagnosis using an alcohol-consumption variable that reflects both alcohol use and abuse. Methods: Data provided by participants in the longitudinal “Outcomes Assessment Project” 12 months after their head and neck cancer (HNC) diagnosis were analyzed using ANOVAs, chi-square tests, and linear and logistic regression analyses. In addition to grouping these patients by self-reported alcohol consumption at 12 months (current, previous, never), these patients were further categorized by whether they were considered problem drinkers or not based on their “Michigan Alcoholism Screening Test” scores. Results: Of the 272 patients in this study, 43.8% were consuming alcohol 12 months after diagnosis. Although current drinkers had higher overall QOL scores and fewer depressive symptoms, a more detailed analysis showed that this trend was only true for current drinkers who did not abuse alcohol. A linear regression analysis demonstrated that the significant, independent predictors of higher overall QOL at 12 months were lower levels of depressive symptoms (p<0.001; coefficient=1.576), lower pain scores (p=0.038; coefficient=0.118), and higher eating scores (p<0.001; coefficient=0.038) at 12 months. A logistic regression analysis demonstrated that type of diet at 12 months (full versus restricted) was the only predictor of continued alcohol use (p=0.002; estimated odds ratio=3.429). Conclusions: The results of this study indicated that overall QOL was influenced not by post-treatment alcohol use but by concurrent levels of depression, pain, and eating function. The patients who were most likely to continue consuming alcohol were those who could, while the patients who were most likely to quit were those with restricted diets and poor oral function. That the strongest deterrent to continued alcohol use was the inability to drink suggests that the relatively high percentage of patients who continue to consume alcohol is lacking either the desire or the ability to quit. Patients with a history of alcohol consumption should be counseled about the detrimental effects of continued alcohol use and should be offered interventions designed to help them quit.

SO35: RECEIPT OF TREATMENT AT HIGHEST VOLUME FACILITIES RESULTS IN BETTER OUTCOMES FOR SURVIVAL IN LARYNGEAL CANCER

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Introduction: Quality of cancer care can be measured by evaluating patient factors, provider factors, and processes of care or facility factors. Little is known about the relationship between the volume of cancer treatment facilities and long-term survival of patients. Objective: This study investigates the relationship between volume of laryngeal cancer care at treatment facilities and five-year survival of laryngeal cancer patients. The hypothesis is individuals who are treated at higher volume treatment facilities have better odds for survival five years after treatment. Methods: 32,502 cases of laryngeal cancer diagnosed during 1996-1998 were abstracted from a hospital-based cancer registry, the National Cancer Database. After censoring cases with missing values for follow-up time and other clinical information, 26,743 cases were included in the final analytic cohort. We identified the number of laryngeal cancer cases treated at each Commission on Cancer facility. Tertiles of the volume variable were created. Univariate and multivariate analyses were performed to evaluate the relationship between volume and other covariates. In addition, proportional hazard survival analysis was performed. Results: Univariate analyses demonstrated that more Stage IV patients, more Medicaid and uninsured patients, and more non-Whites were treated at high volume facilities. Otherwise, survival was not different across tertiles, and the univariate analyses included 32,502 patients from zip codes with higher median annual income (> $45,000) and more high school graduates were treated at low volume facilities. In multivariate analyses, all individuals who had non-private health insurance (uninsured RR = 1.30, p<0.0001, Medicaid RR = 1.57, p<0.0001, Medicare < 65 years RR = 1.66, p<0.0001), who resided in zip codes with fewer high school graduates (RR = 1.08, p<0.0001), and who received treatment in facilities other than the highest volume had higher risk of death (medium volume RR = 1.07, p<0.0001; lowest volume RR = 1.24, p<0.0001). Conclusions: This study is the first to evaluate how volume of multidisciplinary laryngeal cancer care impacts overall five year survival. The only factors in this multivariate analysis associated with increased mortality were having non-private health insurance, residing in zip codes with fewer high school graduates, and receiving care at lower volume facilities. Determining the processes of care factors that are present in the highest volume facilities and implementing them in facilities with lower volume may help narrow the disparities in laryngeal cancer outcomes evident in this analysis.

SO36: DEVELOPMENT OF A PATIENTS CONCERNS INVENTORY (PCI): A WAY OF IMPROVING OUT-PATIENT CONSULTATION & PATIENT EMPOWERMENT

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Objective: The purpose of the Patients Concerns Inventory (PCI) is to allow patients to formulate an individualized profile of their concerns, needs and priorities which can be used on a systematic basis to guide patient consultations and promote multidisciplinary care. The PCI covers a range of issues including hearing, intimacy, fatigue, financial/benefits, PEG tube, relationships, regret, spiritual/religious aspects, support for my family, weight, wound healing. Method: On attending the oncology out-patient clinic patients complete the 45-item PCI together with the University of Washington Quality of Life scale (UW-QOLv4) using a touchscreen computer (TST). Patients are asked to identify any concerns that they wish discussed and this data is networked into the consultation room. In this initial pilot the PCI was used by one consultant in 8 out of 10 weekly clinics between mid-September and early December. There were a total of 127 patients of which 65 completed the PCI. Patients were not recruited if they were pre-treatment, known to have recurrence, or were non-cancer (complex benign). One patient refused. The average time to complete the TST was 8 minutes (range 2 to 23 minutes) and the vast majority found the technology no problem to use. Results: Of the 45 items the most frequently selected by patients were fear of recurrence (38% of patients), dental health/teeth (25%), chewing (20%), saliva (18%), speech (18%), pain in head and neck (15%), swallowing (15%), anxiety (14%), appearance (12%), mood (12%). 80% said that they felt the PCI made a difference (quite a bit / very much) to their consultation as it made it ‘a bit more personal’, ‘reminds them of the points they want discussed’, ‘allows the consultation to get straight to the point’. Although the PCI has the potential to raise a lot of issues its use did not noticeably prolong the consultation. Conclusion: The project is ongoing and data from September 2007 to March 2008 will be presented. This will include details of the case mix of patients, the full PCI response profile, the relationship between the PCI and clinical demographic characteristics and UW-QOL scores. It will also detail the patients feedback from using this approach in routine clinical practice.

OUTCOMES: SURGERY

SO37: THE ROLE OF AGGRESSIVE SALVAGE SURGERY IN TREATING PATIENTS WITH RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Objectives: Several recent studies have placed doubt on the effectiveness of surgical salvage in patients failing first line treatment for head and neck cancer. Because of this and the rise of chemotherapy and re-irradiation protocols for use in recurrent HNSCC, surgery is often not advocated or used in this group of patients. Despite this, it has been our philosophy to treat these patients with aggressive salvage surgery. The aim of this study was to assess the overall survival of patients at our institution who underwent aggressive salvage surgery for recurrent HNSCC. Secondary objectives were to determine if salvage surgery provided a palliative benefit in those patients and to note whether or not recurrent T or overall stage showed any correlation with survival outcomes. Methods: A retrospective chart review was conducted at a tertiary care, regional referral center to identify patients who had undergone salvage surgery for recurrence of HNSCC from 1999 to 2005. 61 patients were identified who met inclusion criteria. Overall sur-
S039: COST-UTILITY ANALYSIS OF CO2 LASER EXCISION VER- 
SUS STANDARD FRACTIONATED EXTERNAL BEAM RADIATION 
(50 GY/4 WEEKS) K.M.Higgins1, D.Enepekides2, 1Sunnybrook Health 
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Methods: With respect to oncologic control six head-to-head comparison 
studies and 22 consecutive case series were identified. All studies were ret- 
rospective. No randomized control trials were identified. The case series 
were pooled as a composite group using a random effects model. The 
analysis was based upon over 7600 patients. Pooled odds ratios (OR) 
and confidence intervals (CI) were calculated. The primary endpoints were local 
control (LC), laryngectomy free survival (LFS), and overall survival (OS). 
For post-treatment voice quality eight studies were identified. Both objective 
and subjective measures of voice quality were used as endpoints. Results: 
There were no significant differences between TOL surgery and XRT with 
respect to LC (OR 0.81, 95% CI 0.51-1.3) and LFS (0.51, 0.32-0.8) and OS (0.66). The 
weighted mean difference for OS was 0.03. For the measures of voice qual- 
y there were no objective differences; however, there was a trend towards 
xpertiority for XRT. Decision tree analysis was then undertaken using the 
base case estimates with mean 5-year local control initial probabilities esti-
mated in figure 4, with rollback calculations performed. CO2 laser cost 
$2475.65 per case, and generated 1.663 QALYs, while radiation therapy 
cost $4965.85 per case, and generated 1.506 QALYs (see Appendix N). This is 
in stark contrast to the initial up-stream treatment costs for each 
respective treatment: CO2 laser ~$1889 per case, and radiation 
~$2454.70 per case. CO2 laser treatment obviously dominates external 
beam radiation from a cost effectiveness/cost utility standpoint primarily 
because of the enhanced downstream affordability of salvage treatment 
found in the CO2 laser treatment pathway. Conclusion: This is the first 
study to examine the management of early stage glottic cancer using sys-
tematic metaanalysis methodology. This metaanalysis shows that there is 
no clear difference in oncologic outcome between TOL surgery and XRT. There 
is, however, a trend for improved post-treatment voice quality with XRT. The 
clinical significance of this is questionable as objective voice analyses often 
do not correlate with subjective quality assessments. Based on the current 
model, CO2 laser delivery dominates external beam radiation and is the 
more cost effective treatment modality in the province of Ontario.

S040: QUALITY OF LIFE IN INDIAN PATIENTS UNDERGOING 
TOTAL LARYNGECTOMY WITH PRIMARY TRACHEO-
ESOPHAGEAL PUNCTURE (TEP) M.S.Deshpande1, D.A.Chaukar1, 
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Background: Cancers of Larynx and Hypopharynx is the second most 
common head neck cancers in Indian patients. Total laryngectomy with or 
without pharyngectomy is the surgery of choice in vast majority of T4 
lesions and in salvage setting. TEP has become a gold standard for voice 
rehabilitation in the post-laryngectomy setting. Recent trends have witnessed 
incorporation of TEP as an irreplaceable armamentarium in voice rehabili-
tation of patients in Indian population, mainly owing to increased patient 
awareness, surgical expertise and improved speech rehabilitation. The 
impact of such comprehensive voice rehabilitation on the quality of life out-
comes in the Indian population was studied. Objective: To study the impact 
of Total laryngectomy with TEP on health related QOL in Indian sub- 
jects. Design: A longitudinal prospective cross sectional cohort study. 
Materials and Methods: A cross-sectional study was undertaken to 
assess QOL in patients undergone total laryngectomy with primary TEP. 
One hundred thirty two patients were presented with EORTC-QLQ-C30 & 
QLQH&N-35 questionnaires that were translated into two vernacular lan-
guages [Hindi and Marathi], for which validity and reliability analysis had 
been performed. The questionnaire was served a by the study coordinator. 
Statistical analysis was performed using SPSS software. Results: One hundred 
three patients filled the questionnaires. Forty-one patients (33.6%) filled English, 58 patients (47.5%) filled Hindi and 23 patients (18.9 %) filled Marathi questionnaire. The median duration from 
laryngectomy was 21.3 months (range 3.6-161 months). The results from 
the EORTC-QLQ-C30 showed Good mean scores (>70) on function scales 
in physical (mean 81), role (mean 82), emotional (mean 79), cognitive
Patients with SCC of the oral cavity, oropharynx and larynx treated by primary resection were identified. Pathology slides from the resection specimens were reviewed and a risk assessment model (RAM) was applied. Validation of our risk assessment model (1) is the next step towards the demonstration of its predictive power in a low-stage cohort. We present an interim analysis on 200 patients. Methods: Patients with SCC of the oral cavity, oropharynx and larynx treated by primary resection were identified. Pathology slides from the resection specimens were reviewed and a risk score was generated. Kaplan-Meier analyses with time-to-events (disease progression, overall survival (OS)) and Cox regression analyses were performed. Results: This group consists of 200 patients, ages 25-95 (median 63 years), with primary SCC of the oral cavity (98), oropharynx (46) and larynx (56). Stage I/II and Stage III/IV patients comprised 34% and 66% of this group respectively. The distribution of low-, intermediate-, and high-risk groups was 14%, 41% and 45%, respectively. Follow-up time for all patients is 0-153 months, mean of 16 months. The median OS for low-, intermediate-, and high-risk patients is 65, 66, and 31 months, respectively. The high-risk category is predictive of decreased OS time compared to intermediate and low-risk categories (p = 0.0004). Regression analysis examined the impact of clinicopathologic confounders; T and N stage, adjuvant therapy, age and gender, did not impact this model after the addition of the high-risk category. The high-risk category approached statistical significance as a predictor of decreased overall survival in regression analysis (Hazard ratio [HR] = 2.6, p = 0.08). Stage and age were found to be strong predictors of OS. Kaplan-Meier survival analysis for patients with intermediate and high-risk disease showed a significantly decreased survival compared to low-risk disease (p < 0.0001). Conclusion: Laryngeal carcinomas are associated with an overall better survival than oral cavity/oropharynx SCC. Thus it may be important to validate the risk model by separate tumor sites. Disease-progression status was known on 196 patients. The high-risk category is predictive of decreased time to disease progression as compared to intermediate and low-risk categories (p = 0.001). Median time to disease progression for intermediate- and high-risk patients is 17.5 and 8.5 months, respectively. Regression analysis revealed that T and N stage, adjuvant therapy, margin status, age and gender did not impact this model after the addition of the high-risk category. The high-risk category was predictive of disease progression when adjusted for confounders (HR 7.58, p = 0.052). Tumor site did impact this model, but not to the same degree as was seen for OS (HR = 0.89, p = 0.76). Conclusion: Preliminary analysis on this ongoing validation study is limited by a short median follow-up period. The classification of patients as high-risk appears to be a promising prognosticator, when adjusted for tumor site and stage. The impact of tumor status on the outcome model indicates that future risk analyses should be performed in a tumor site-specific manner.

S042: OUTCOME OF PATIENTS TREATED SURGICALLY FOR LYMPH NODE METASTASES FROM CUTANEOUS SQUAMOUS CELL CARCINOMA

Background: Lymph node metastasis from cutaneous squamous cell carcinoma (cSCC) of the head and neck is uncommon. Scant data exists on the outcome of this select group of patients. The purpose of this study was to investigate the survival of patients treated surgically with or without radiation therapy for lymph node metastasis from cSCC. Methods: Patients from a tertiary-care referral hospital and adjacent Veteran’s Administration medical center with pathologic evidence of cervical lymph node metastasis from cSCC of the head and neck were entered into a database starting in 1995. Follow-up was performed for 60 months. Clinicopathologic data were abstracted for all patients treated surgically for lymph node metastases from cSCC and analyzed using COX multivariate analysis controlling for age, presentation (primary v. recurrent), immune status and adjuvant radiation therapy. Results: Sixty-five patients with lymph node metastasis from cSCC of the head and neck were identified. Ten patients who received only palliative care were excluded from the analysis. Among the 55 (51 male, 4 female) patients treated surgically with curative intent, the median age was 73 years. Tumor stage was unknown for most patients. Of the remaining, eighteen (32.7%) patients presented with T0-T2 stage disease; five (9.1%) T3-T4. Thirty six (65.5%) patients were treated for recurrent disease and 10 (18.2%) patients were chronically immunosuppressed. The most common procedures were neck dissection and parotidectomy in 48 (87%) and 42 (76.4%) patients, respectively. Forty-two (76.4%) patients received radiation therapy. The median overall survival was 31 months with an estimated 3-year survival of 36%. Using COX multivariate analysis, immunosuppression was associated with a significantly higher risk of death (Hazard ratio, 3.5; 95% CI 1.1-11.2). Conversely, adjuvant radiation therapy was associated with a reduced risk of death (Hazard ratio, 0.3; 95% CI 0.1-1.0). Conclusions: Lymph node metastasis from cSCC of the head and neck is associated with poor survival despite aggressive surgical treatment with or without radiation therapy. Patients with chronic immunosuppression are at greatest risk of death and warrant further investigation.

S043: POORER OUTCOMES FOR YOUNGER PATIENTS WITH ORAL CANCER

Background: Over the last two decades there has been an increase in the incidence of squamous cell carcinoma of the oral cavity (OSCC) in younger patients. This trend has been reported by investigators in both the United States and Europe. The outcome of younger as compared to older patients with oral cavity cancer remains controversial. Methods: Using data from the Surveillance, Epidemiology and End Results (SEER) program we studied cases of OSCC occurring in patients greater than 20 years of age and diagnosed from 1973-1999 (n=19,681). We studied four cutoffs for defining younger patients: 40, 45, 50, and 55 years. Group control of younger patients were retrospectively matched on gender, race, cancer subsite of disease, age and diagnosed from 1973-1999 (n=19,681). We studied four cutoffs for defining younger patients: 40, 45, 50, and 55 years. Group control of younger patients were retrospectively matched on gender, race, cancer subsite, stage, and site of disease. The five-year overall survival for patients with cancer of different oral cavity subsites was studied for patient groups as various ages in a Kaplan-Meier survival analysis (Kaplan-Meier method). Intercensal death rates for survival were used as the log rank test. Results: Overall, younger patients were more likely to be male, black, have local disease, and have cancer of the tongue. These differences were in part reflected in a significantly poorer five-year survival for younger patients (Age 40: 89.9 vs. 91.4%, p<0.001; Age 45: 89.0% vs. 91.6%, p<0.0001; Age 50: 89.2% vs. 91.8%, p<0.0001; Age 55: 89.3% vs. 92.2%, p<0.0001). Propensity score matching produced matched groups with similar distribution of patient and disease characteristics. Even in these matched groups, younger patients still had a significantly poorer survival (Age 40: 90.5 vs. 91.1%, p=0.14; Age 45: 89.9% vs. 91.6%, p=0.012; Age 50: 90.1% vs. 92.1%, p<0.0001; Age 55: 89.3% vs. 92.0%, p<0.0001). Conclusions: Younger patients diagnosed with OSCC had a poorer overall five-year survival rate, even after controlling for gender, race, subsite of disease occurrence, and stage of disease. These results contrast with recent results using population based data that suggest better overall survival in younger patients.

S044: FIVE YEAR OUTCOME DATA IN ORAL AND OROPHARYNGEAL CANCER - A COHORT OF 500 PATIENTS PRESENTING OVER A TWO YEAR PERIOD

Background: Lymph node metastasis from cutaneous squamous cell carcinoma (cSCC) of the head and neck is uncommon. Scant data exists on the outcome of this select group of patients. The purpose of this study was to investigate the survival of patients treated surgically with or without radiation therapy for lymph node metastasis from cSCC. Methods: Patients from a tertiary-care referral hospital and adjacent Veteran’s Administration medical center with pathologic evidence of cervical lymph node metastasis from cSCC of the head and neck were entered into a database starting in 1995. Follow-up was performed for 60 months. Clinicopathologic data were abstracted for all patients treated surgically for lymph node metastases from cSCC and analyzed using COX multivariate analysis controlling for age, presentation (primary v. recurrent), immune status and adjuvant radiation therapy. Results: Sixty-five patients with lymph node metastasis from cSCC of the head and neck were identified. Ten patients who received only palliative care were excluded from the analysis. Among the 55 (51 male, 4 female) patients treated surgically with curative intent, the median age was 73 years. Tumor stage was unknown for most patients. Of the remaining, eighteen (32.7%) patients presented with T0-T2 stage disease; five (9.1%) T3-T4. Thirty six (65.5%) patients were treated for recurrent disease and 10 (18.2%) patients were chronically immunosuppressed. The most common procedures were neck dissection and parotidectomy in 48 (87%) and 42 (76.4%) patients, respectively. Forty-two (76.4%) patients received radiation therapy. The median overall survival was 31 months with an estimated 3-year survival of 36%. Using COX multivariate analysis, immunosuppression was associated with a significantly higher risk of death (Hazard ratio, 3.5; 95% CI 1.1-11.2). Conversely, adjuvant radiation therapy was associated with a reduced risk of death (Hazard ratio, 0.3; 95% CI 0.1-1.0). Conclusions: Lymph node metastasis from cSCC of the head and neck is associated with poor survival despite aggressive surgical treatment with or without radiation therapy. Patients with chronic immunosuppression are at greatest risk of death and warrant further investigation.

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Introduction: The West of Scotland has the highest prevalence of head and neck cancer in the United Kingdom. The overwhelming majority of cases are managed by the National Health Service providing an opportunity to gather comprehensive data on a cohort of patients and determine outcome. Methods: Between November 1999 and November 2001 data was prospectively gathered on all patients in Scotland presenting to an NHS hospital with non-cutaneous head and neck cancer. Case ascertainment was aided by a listing of new referrals in hospital pathology departments throughout Scotland. Comprehensive demographic data, site, stage, treatment intent, as well as surgery, radiotherapy, and chemotherapy details were prospectively entered onto a database. This study focuses on patients presenting with oral and oropharyngeal cancer in the West of Scotland (Population 2.5 million). Long-term follow-up information was derived from scrutiny of case notes, locally held databases, and the Scottish death registry. The Kaplan-Meier method was used to estimate survival and parametric data were compared with the log rank test. Prognostic factors significantly influencing survival on univariate testing were entered into a Cox regression model to determine independent influences on outcome. Results: A total of 500 patients with 508 oral or oropharyngeal cancer presentations entered this study. A total of 170 patients had squamous cell carcinoma as their tumour type. Of these 100 patients were not suitable for treatment with curative intent. Co-morbidity appeared to be at least as important as advanced stage disease in deciding treatment intent. Amongst this group provision of palliative treatment (principally radiotherapy and chemotherapy) prolonged life from a median of 2.5 months for best supportive care to a median of 5 months where treatment was given. For treatment intent the 5-year specific survival was 66% for the oral cavity and 62% for the oropharynx. Overall survival for the two sites was identical at five years (42%). On multivariate analysis nodal status and perineural invasion were of independent prognostic significance. Conclusions: Surgery and post-operative radiotherapy are effective treatment modalities for a majority of patients presenting with oral and oropharyngeal cancer. Trial data continue to emerge demonstrating improved outcomes using newer, and usually more intensive treatment regimens. The majority of studies however stipulate an ECOG/WHO performance status of 0 or 1. This study highlights the prevalence of co-morbidity in many head and neck cancer populations and its significant influence on management decisions. It seems unlikely therefore that the improved outcomes observed in clinical trials will translate directly into similar improvements when applied to a non-trial population such as that seen in the West of Scotland. The use of intensified treatment regimens is likely to be toxicity limited where co-morbidity is more prevalent.

SO46: DAHANCA 10 - A RANDOMIZED STUDY OF ARANESP AS MODIFIER OF RADIOTHERAPY IN PATIENTS WITH PRIMARY HNSCC

Aim: The primary objective was to evaluate, in an open randomized trial, if correction of low hemoglobin (Hb) levels by means of the novel erythropoiesis stimulating protein: darbepoetin alpha (Aranesp®) during radiotherapy improves outcome of curative treatment in patients with HNSCC. Following a planned interim analysis which showed inferiority of the experimental treatment, the trial was stopped in November 2006, and subjected to the following analysis which was performed per December 1, 2007. Patients and Methods: Pts with HNSCC eligible for primary radiotherapy alone (except those with T1 glottic cancers) and with Hb values below 9.0 mmol/l (14.0 g/dl) were randomized to receive Aranesp® together with accelerated (6 weekly fractions) fractionated radiotherapy (66-68 Gy in 33 to 34 fx). In addition, patients were also treated with the hypoxic radiosensitizer Nimorazole. Aranesp® was given subcutaneously in a dose of 150 micrograms. The first dose was administered the week prior to start of radiotherapy and continued weekly until completion of radiotherapy, or stopped earlier if the Hb exceeded 9.6 mmol/l (15.5 g/dl). Pts were recruited from 110 Danish and 10 Norwegian centres from the Norwegian Radium Hospital in Oslo. Results: In total, 522 patients had been randomized at the time of the interim analysis with a median follow-up time of 42 months (range 13-64). Of these 514 were eligible for analysis (255 pts treated with Aranesp® and 259 pts in the control group). Among these, 170 have experienced a loco-regional failure (the primary study endpoint). There have been 232 deaths of which 171 are known to be of the cancer in question. The patients were evenly distributed according to the stratification parameters (gender, T and N staging, tumor site, institution) which, except the latter, were also found to significantly discriminate prognosis within the material. Aranesp® resulted in the expected increase in Hb with more than 91% of the patients obtaining the planned increase. The compliance to Aranesp® was good, but with a slight excess incidence of serious (cardiovascular) adverse events (3% vs. 1%) for the Aranesp® vs. control arm. Overall, the results showed a poorer outcome in 5-year actuarial loco-regional control (59% vs. 68% (p=0.03, RR: 1.38 [1.01-1.88]) for the Aranesp® vs. control arm. This was also seen for the endpoint of disease-free survival (36% vs. 46%, p=0.04, RR: 1.29 [1.01-1.65]). The difference in tumor control resulted in a similar difference in 5-year disease-specific survival (54% vs. 67%, p=0.05, RR: 1.34 [1.00-1.82]), whereas there was no significant difference in overall survival (39% vs. 51% for Aranesp® and control respectively. p=0.14, RR: 1.21 [0.97-1.57]). There were no apparent differences in acute or late radiation related morbidity. All univariate analyses were confirmed in a multivariate setting. Conclusion: Correction of the Hb level with Aranesp® in patients with HNSCC resulted in a significantly poorer tumor control after radiotherapy. The treatment principle was abandoned and the difference in outcome is being subjected to further examination.
Background: VEGF expression has been shown to be up-regulated in SCCHN, representing a promising therapeutic target. Bevacizumab is an anti-VEGF monoclonal antibody that may potentiate the efficacy of concurrent radiation and docetaxel. This trial represents the first attempt, to the best of our knowledge, to establish the efficacy and toxicities of the addition of bevacizumab to concurrent radiation with docetaxel in patients with locally advanced SCCHN. Methods: Patients with previously untreated stage III-IVB SCCHN receive standard once-daily radiation (70.2Gy, 1.8Gy/day), weekly docetaxel (20 mg/m2/week for the duration of radiation) and biweekly bevacizumab (5 mg/kg/two weeks) during and for up to one year following radiation. A total of 30 patients will be enrolled in this study. Results: A total of 23 patients (20 males, 3 females), mean age 56.3 years (range 48-73), all with stage IV disease have been enrolled. Primary site: pharynx (n=17) and larynx (n=6). 21 patients have completed concurrent chemoradiation. After a median follow up of 9 months (range: 0 - 23), 17 patients remain in complete response, 4 patient developed metastatic disease and two of them died. The estimated one-year survival is 89.0% (95% CI 0.64 to 0.97). The estimated one-year progression-free survival is 0.78 (95% CI, 0.50 to 0.91). 8/21 patients underwent planned neck dissection and they all had a pathologic complete response. 4/17 patients, in complete response, are currently receiving adjuvant bevacizumab. No unexpected toxicities were encountered during chemoradiation. No episodes of severe bleeding noted. No healing complications observed after planned neck dissections. Conclusions: For patients with locally advanced SCCHN, preliminary data suggest that the addition of bevacizumab to concurrent radiation with docetaxel is feasible, safe and active. Supported in part by Genentech, NIH grants CA62502 and M01 RR-000080, Clinicaltrials.gov identifier: NCT00281840.

SO48: PHASE I STUDY OF ERLOTINIB WITH DOCETAXEL AND RADIATION IN LOCALY ADVANCED HEAD AND NECK SQUAMOUS CELL CANCER (SCCHN) P.Savvides1, A.Argiris1, J.Greskovich2, J.Bokar1, S.Agarraviga3, R.Rezaee5, M.Schuchter5, J.Wasman5, R.Rezaee6, P.Lavertu5, 1Case Comprehensive Cancer Center, Cleveland, OH; 2Medical College of Georgia, Augusta, GA; 3University of Minnesota, Minneapolis, MN; 4University of Pittsburgh Medical Center, Pittsburgh, PA; 5Medical College of Georgia, Augusta, GA; 6St Luke’s Hospital and Health Network, Bethelhem, PA; 7Case Comprehensive Cancer Center, Cleveland, OH; 8University of Washington, Seattle, WA; 9Mary Babb Randolph Cancer Center, Morgantown, WV

Background: EGFR is highly expressed in SCCHN, representing a promising therapeutic target. Erlotinib (E) is an EGFR tyrosine kinase inhibitor that may potentiate the efficacy of concurrent radiation (RT) and docetaxel (D). We sought to establish the MTD, toxicities and preliminary efficacy of the combination of RT, D and E in patients (pts) with SCCHN. Methods: Patients with previously untreated stage III-IVB SCCHN were enrolled in a phase I dose-escalating study with standard once-daily RT (70.2Gy, 1.8Gy/day), weekly D for the duration of RT and daily E for two weeks prior, during and up to two years following RT. 4 dose levels (DL) were evaluated [D (mg/m2)/E (mg): 15/50, 15/100, 20/100, 20/150]. A 3+3 escalation design was followed. Pharmacokinetic studies (PK) were performed. Results: A total of 24 patients were enrolled (6 pts at each dose level). Primary site: oral cavity (n=11), pharynx (n=15) and larynx (n=8). 20 patients (83%) had stage IV disease. Three dose-limiting toxicities were observed, 1 at each dose level (1-3), including a death within 30 days from last treatment (DL1), grade 3 mucositis resulting in holding RT (>5 days) (DL2) and grade 4 mucositis (DL3). No dose-limiting toxicities occurred on dose level 4. Best response was noted in 20 of 24 evaluable pts (n=1) at death on study (n=1). Of the five total deaths observed to date, four occurred in the lowest dose level (DL1), and one was observed in DL2. No deaths have been observed as yet in the two highest dose levels. Estimates of 1-year overall survival for the 4 sequential dose levels are 50% (DL1), 83% (DL2) and 100% (DL3). Three patients died at the DL2 dose level (n=1) and at DL1 (n=2). Of the five total deaths observed to date, four occurred in the lowest dose level (DL1), and one was observed in DL2. No deaths have been observed as yet in the two highest dose levels. Estimates of 1-year overall survival for the four sequential dose levels are 50% (DL1), 83% (DL2) and 100% (DL3) (in DL 3 and 4). Interpatient variability of E peak plasma concentrations measured after the CR were observed at all dose levels (expressed as mean ± s.d.): 458 ± 173 ng/mL (150 mg dose, DL1), 851 ± 341 (100 mg dose, n=12, Dls 2-3), 1126 ± 259 (150 mg dose, n=6, DL4). Adjuvant erlotinib plasma concentration data will be presented separately. No significant PK interaction of erlotinib with docetaxel was noted. Conclusions: Results of the completed phase I trial evaluating the combination of daily erlotinib with weekly docetaxel and RT for pts with stage III-IVB SCCHN are presented, demonstrating that the combination is feasible and highly active. Erlotinib at full dose (150 mg daily) and Taxotere (20 mg /m2 weekly during radiation therapy) is the selected dose for the phase II multicenter clinical trial, currently accruing patients.

SO49: TUMOR VOLUME AS OUTCOME PREDICTOR IN CHEMORADIATION FOR ADVANCED HEAD AND NECK CANCER J.Kriegers1, F.Pameijer1, A.Balm1, M.Hauptmann1, F.Hoebers1, C.Rasch1, 1Netherlands Cancer Institute, Amsterdam, The Netherlands

Objective: Concomitant chemoradiation (CCRT) is considered the standard of care for advanced head and neck squamous cell carcinoma (HNSCC). This treatment is associated with a high degree of toxicity and serious side effects. Selecting patients that are likely to benefit most from this intensive treatment is therefore essential. Current patient selection is based on TNM stage. However, TNM based outcome is highly dependent on treatment modality and may be insufficient in new multimodality treatment regimens. This stresses the need for new prognostic factors. An earlier report demonstrated a significant impact of primary tumor volume on outcome for intra-arterial chemoradiation (van den Broek et al., Cancer 2004). The purpose of the present study was to analyze the prognostic value of primary tumor volume in a large series of patients with advanced HNSCC and treated with various CRT regimens. Methods: 371 patients, treated with CCRT for advanced HNSCC and a pretreatment MRI or CT scan were selected. Primary tumor site distribution was oral cavity 82 (22.1%), oropharynx 226 (60.9%) and hypopharynx 63 (17.0%). T and N stage distribution was T2 14 (3.8%), T3 113 (30.5%), T4 244 (65.8%), N0 75 (20.2%), N1 49 (13.2%), N2 214 (57.7%) and N3 33 (8.9%). Patients were treated with 4 different CRT regimens. Radiotherapy (70Gy/35 fractions in 6 weeks) was combined with either 4 courses of intra-arterial cisplatin (n=178), 3 courses of intravenous cisplatin (n=88) or 20-25 daily courses of low-dose cisplatin (n=46). The remainder of the patients (n=59) was treated with a CCRT regimen consisting of 5 to 6 weekly courses of intravenous cisplatin and concomitant accelerated radiotherapy (68 Gy/34 fractions in 5.5 weeks). All patients were treated with curative intent. The MRI (n=283) or CT (n=88) scan was used to delineate all visible primary tumor tissue and the corresponding tumor volume was calculated. Median follow-up was 32.3 months. Results: Primary tumor volume ranged from 2.1 cm3 to 393.8 cm3. The mean and median tumor volumes were 37.6 cm3 and 28.2 cm3 respectively. For the entire group the 5-year local control and overall survival rates were 67.8% and 37.9% respectively. Patients with a small tumor, defined as a tumor volume equal to or below the median volume, had a significantly better 5-year local control rate (78.3% vs. 51.3%, p<0.0001). The five-year overall survival rate was also significantly better in patients with a small tumor (56.4% vs. 26.0%, p<0.0001). In a multivariable analysis including other known prognostic factors, tumor volume was a highly significant, independent predictor for both local control and overall survival whereas T- and N-stage were not. Conclusions: This study demonstrates a significant correlation between primary tumor volume and outcome. We established tumor volume to be a more important prognostic factor for local control and overall survival than T or N stage. Pretreatment evaluation of primary tumor volume may contribute to a better selection of head and neck cancer patients for intensive CCRT.

S050: DOES POST-TREATMENT SURVEILLANCE IMPROVE SURVIVAL IN HEAD & NECK CANCER PATIENTS? D.O Francis1, E.A.Weymouth1, T.Vaughan1, B.Yueh1, 1University of Washington, Seattle, WA; 2University of Minnesota, Minneapolis, MN

Objectives: After treatment for head and neck cancer, routine surveillance has been advocated to identify early persistent disease, recurrent disease, and second primary tumors because of the belief that early detection offers better opportunities for salvage. However, little evidence supports the effectiveness of surveillance in improving subsequent survival. We sought to use a population-based study to evaluate whether more intensive surveillance strategies improve survival. Methods: This retrospective cohort study identified patients with recurrent squamous cell carcinoma diagnosed between 1991 and 1999 in the Surveillance Epidemiology and End Results Tumor Registries (SEER). Medicare claims were linked to track surveillance visits. The American Medical Association Physician Masterfile was linked to gather information on treating physicians. Using these three large datasets, we created a cohort of 2,629 patients with ‘subsequent disease’ (recurrent, persistent, or second primary tumors). Demographic, cancer, treatment, physician, and surveillance-related variables were analyzed for their impact on vital status. Proportional hazards modeling was used to evaluate the inde-
Of 2,629 patients who developed subsequent disease, 50% were diagnosed within a year of initial treatment. There was substantial variation in the absence of surveillance visits, ranging from no surveillance (60%) to using more visits than recommended by the 2002 National Comprehensive Cancer Network/American Head and Neck Society (NCCN/AHNS) Consensus recommendations. Multivariable regression revealed that hypermethylation informative tumor revealed that 11 patients had hypermethylation informative tumor as an independent prognosticating factor for HPV16 positive patients who have no smoking history. Of the smokers, HPV16 associated HNSCCs display a pattern of genetic alterations (loss and gain) different from those of HNSCCs without HPV 16 DNA. Methods: Saliva was collected from 45 HNSCC patients and 21 control subjects. HPV in saliva DNA was detected by single-round PCR using consensus primers MY09/11 from the L1 gene region. HPV was typed by two-round PCR using primers located in the E6/E7 gene region and specific for types 16, 18, and 33. PCR products were electrophoresed through 2% agarose, stained with ethidium bromide and visualized with a GelsdocXR imaging system. In a subset of 27 HNSCC patients, genetic alterations were evaluated in the saliva DNA using multiplex ligation probe amplification (MLPA) assay to interrogate 82 genes with known association with HNSCC. Results: HPV was detected in the saliva DNA from 17 of 45 (38%) HNSCC patients and in 1 of 21 (5%) control subjects. Sixty percent identified HPV type 16 in twelve (27%) HNSCC patients and in none of the controls. HPV type 33 was identified in 5 of 45 (11%) HNSCC patients and in 1 of 21 controls (5%). Statistically significant association of HNSCC with saliva HPV (p=0.006) and HPV type 16 (p=0.007) but not HPV type 33 (p=0.656) was found (Fisher's Exact test). Of the 82 genes interrogated in the subset analysis, there was statistically significant association between TP53 gene loss and HPV 16 positivity (p=0.049) Fisher's Exact test. In the subset of TP53 seen in 45% of HPV 16 positive HNSCC patients in comparison to 13% of HPV 16 negative cases. Conclusions: Detection of HPV in saliva is significantly associated with HNSCC. HPV subtype analysis using saliva DNA showed significant association of HPV type 16 with HNSCC but not HPV type 33. Allelic loss of TP53 gene showed significant association with the HPV 16 positivity. This study supports clinical use of saliva for concomitant non-invasive molecular detection of HPV16 and gene alterations to identify highly relevant signature clonal biomarkers using high throughput assays for head and neck cancer screening, surveillance and future therapeutic strategies like HPV vaccines, overcoming the need for tissue acquisition via invasive surgical procedures. Additionally this study will also help in understanding the biological etiopathogenesis of HNSCC.
HPV16 positive never smokers had a significantly better (P < 0.05) overall and disease-specific survival (and borderline recurrence-free survival) over either HPV16 positive smokers or HPV16 negative patients. **Conclusions:** Our data suggests that HPV16 positive SCCOP patients tend to be younger, non-smokers and non-drinkers. Although these patients tend to present with more advanced, more poorly differentiated disease, HPV16 positive never smokers seem to have a significant survival advantage. Our findings strengthen the argument for an alternate, HPV16 driven carcinogenic pathway with a unique characteristics possibly including better response to treatment. Of our HPV16 positive patients, those with a smoking history did not share the survival benefit seen in never smokers, and these individuals may have a more complex disease involving multiple carcinogenic pathways. The mechanisms underlying these survival differences need to be explored in future research.

**CLINICAL: NECK I/SENTINEL NODE**

**S055: RELATIVE EFFICACY OF HISTOPATHOLOGY, IHC AND RT-PCR FOR THE DETECTION OF OCCULT METASTASIS IN SENTINEL LYMPH NODES**

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**Background:** Sentinel lymph node biopsy is emerging as an effective tool to identify occult metastasis in oral squamous cell carcinoma. There is however no consensus in the choice of laboratory method for analyzing the nodes to identify occult metastasis. **Objectives:** The objectives of this study was to determine relative efficacy of identifying occult metastasis by frozen section, imprint cytology, histopathology of single section, histopathology following step sectioning, Immunohistochemistry for pan-Cytokeratin and DiG3 and RT-PCR for CK-14 and E1f4. **Method:** Patients with T1, T2, NO oral squamous cell carcinoma were enrolled in a prospective clinical trial to determine the relative efficacy of identifying occult metastasis by different pathological and laboratory assays. Sentinel lymphnodes were localized preoperatively by lymphoscintigraphy and intra-operatively by hand held gamma probe. The sentinel lymph nodes were bisected longitudinally through the hilum and one half is subjected to imprint cytology, frozen section, histopathology of single section through the hilum, serial step sectioning at 2mm interval with Hematoxylin and eosin staining (H&E) and immunohistochemistry (IHC) on alternate sections for pan-Cytokeratin and DiG3. In H&E negative nodes, RNA is extracted and presence of occult metastasis was determined by RT-PCR for CK-14 and E1f4. **Results:** Total of 55 patients were accrued, sentinel lymph node localized in all patients. In 3 patients level 1 node was not localized at the time of surgery. Number of SLN isolated per patient ranged from 1 to 4 (mean 2.6); yielded a total of 141 SLN from 55 patients. Frozen sections and imprint cytology was positive for metastasis in 7 patients. Routine H&E using single section identified metastasis in 8 patients. SSE and H&E increased the yield to 13 and SSS and IHC in 16 patients. Of these patients 5 had macro-metastasis (>2mm), 6 had micro-metastasis (<2mm), 2 had isolated tumor cells and 3 patients had single cell deposits. Macro-metastasis were identified by all investigations modalities, micro-metastasis was missed by routine pathology in 3 cases, which were picked by SSS. Isolated tumor deposits were picked only by SSS. Single cells were identified only by IHC. SLN of 47 patients who were found to have no metastasis by standard H&E were subjected to molecular assay for presence of CK-14 and eif4, which identified occult metastasis in 10 additional patients. **Conclusion:** Sentinel node biopsy detected occult metastasis in neck in 16/55 patients in T1, T2 oral squamous cell carcinoma. Imprint cytology was as good as frozen section in identifying occult metastasis; however metastasis was missed in 1 patient, which was picked by the standard histopathology. SSS could pick metastasis in 8 additional patients. SSS with H&E is as effective as SSS with IHC for the detection of Macro metastasis. However micro metastasis and isolated tumor cell can be detected only by SSS and IHC. RT-PCR was most sensitive in detecting occult metastasis. The clinical significance of micrometastasis, isolated tumor cells and RT PCR detected metastasis needs to be determined.

**S056: THE IMPORTANCE OF IMMUNOHISTOCHEMISTRY IN SENTINEL LYMPH NODE ANALYSIS IN HEAD AND NECK CANCER**

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**Background:** Accurate staging of sentinel lymph node histopathological status is critical and the histopathological exam should evaluate the presence of neck lymph node metastases for treatment and prognosis purposes. Hematoxylin-eosin (H&E) staining is the usual method in sentinel lymph node analysis. Other techniques as immunohistochemistry, step serial section and molecular pathology could improve the diagnosis of metastatic lymph nodes. The objective of this study is to evaluate the negative predictive value of HE staining compared to immunohistochemistry and step serial section analysis in sentinel lymph node in head and neck squamous cell carcinoma (SCC). **Methods:** Patients with oral, lip, oropharynx and larynx SCC underwent surgical procedure for tumor resection and sentinel lymph node sampling, with a total of 68 necks studied. The sentinel lymph node samplings which resulted negative by HE method were also submitted to immunohistochemistry and step serial section analysis. **Results:** From 68 evaluated necks, 58 were considered free from disease by HE exam. The immunohistochemistry and step serial section analysis confirmed the presence of metastasis in 2 of 58 (3.5%) cases despite they were negative on HE evaluation. **Conclusion:** The negative predictive value of HE histopathological method in this study was 96.5% when compared to immunohistochemistry and step serial section exam.

**S057: SENTINEL NODE BIOPSY IN ORAL/OROPHARYNGEAL SQUAMOUS CELL CANCER: FIVE YEAR FOLLOW-UP**

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**Objective:** The most important predictor of prognosis in patients with cT1/T2 oral or oropharyngeal squamous cell carcinoma is involvement of the cervical lymph nodes. Elective neck dissection (END) provides staging information and treatment for the involved neck, but is unnecessary in three-quarters of cNO patients. This study aims to ascertain whether sentinel node biopsy can accurately stage the cN0 neck, while avoiding the morbidity associated with neck dissection for those patients found to be sentinel node negative. **Methods:** 227 Sentinel node biopsy procedures were carried out across 6 European institutions between 1998 and 2002. Of these, 134 cT1/T2 cN0 patients met the inclusion criteria for the study. Seventy-five patients underwent sentinel node biopsy assisted elective neck dissection (SNB+END), with 59 patients undergoing sentinel node biopsy alone. Sentinel node positive patients went on to receive therapeutic neck dissection. All harvested sentinel nodes were evaluated using the full pathological protocol of haematoxylin-eosin staining (H&E), step-serial sectioning and immunohistochemistry (IHC). Mean follow-up was 5.5 years. **Results:** Sentinel node(s) were successfully located and harvested in 125/134 patients (93%). Forty-two of 125 patients were upstaged by sentinel node biopsy. 10 of these 42 patients had occult metastasis, confirmed by histopathology and step serial section analysis. Other techniques as immunohistochemistry, step serial section and histology was positive in 10 patients. Of these patients, 7 had macro-metastasis (>2mm), 2 had micro-metastasis (<2mm), 1 had isolated tumor cells and 3 patients had single cell deposits. **Conclusion:** Sentinel node biopsy accurately predicts the disease status of the remaining cervical lymph node basin in patients with early head and neck squamous cell cancer, and has the added advantage of allowing in-depth evaluation of harvested nodes by step-serial sectioning and immunohistochemistry. It can be used as a staging tool in this patient group, without adversely affecting patient outcomes. However, caution may be required when applying this technique to patients with tumours in the floor-of-mouth.

**S058: SENTINEL NODE BIOPSY FOR STAGING OF ORAL CANCER - AN ANALYSIS OF CLINICOPATHOLOGIC FACTORS**

**T.R. Loree1, M.S. Burke1, S. Popat1, M. Merzianu1, W.L. Hicks Jr1, N.R. Rigual1, Roswell Park Cancer Institute, Buffalo, NY**

**Objective:** The importance of accurate disease staging in squamous cell carcinoma (SCCA) of the oral cavity has been well documented with respect to both therapeutic decision making as well as prognosis. Early detection of lymph node (LN) metastases offers the opportunity for more timely intervention, which may prevent morbidities and improve outcome. Neck staging is typically accomplished with selective neck dissection (SNND). This results in significant morbidities and over treatment of the majority of patients who remain NO. We report the accuracy of sentinel node biopsy (SNB) and patient outcomes as well as clinicopathologic tumor factors associated with neck metastases. **Methods:** From 2000 to 2007, data
was collected prospectively for patients with T1-T3 SCCA of the oral cavity and clinically N0 necks. 27 patients underwent synchronous SNB and elective neck dissection, whereas 24 patients underwent SNB followed by therapeutic neck dissection only if sentinel node(s) were positive on final pathology. Sentinel LNIs were fixed in 10% buffered formalin, sectioned at 2-3mm intervals and examined with Hematoxylin-Eosin (H&E) stain at each of three intervals. Non-sentinel nodes (from neck dissection specimens) underwent routine processing with H&E stain and immunohistochemical staining. Pathologic staging was compared to clinical stage as well as correlated with tumor size, grade, thickness, and presence of lymphovascular invasion. Follow-up ranged from 1-84 months (mean 37 months).

Results: There were 34 males and 17 females, ages 38-81 years (mean 61 years). 9/51 (18%) were T1N0, 39/51 (78%) were T2N0, and 3/51 (6%) were T3N0. 27/51 (53%) had SLB followed by neck dissection. 24/51 (47%) had SNB only initially, with 3/24 requiring therapeutic neck dissection at a later date. At least one sentinel LN was identified in 47/51 patients. Upstaging occurred in 17/51 (33%). The risk of occult metastases was 9% (1/11) with well differentiated tumors, 29% (9/31) for moderately, and 78% (7/9) for poorly differentiated (p=0.004). Tumor thickness less than 6mm had 11% (3/27) risk of occult nodal involvement vs. 58% (14/24) for those greater than 6mm (p=0.0004). Presence of lymphovascular invasion increased risk of occult nodal involvement from 23% (10/43) to 88% (7/8) (p=0.001). Of the 47 patients with identified LN, there were no false positives and 3 false negatives. Sensitivity of SLB = 81%, specificity = 100%, accuracy = 94%, negative predictive value = 91%.

Conclusions: In our series 33% of patients who were N0 clinically had occult LN metastases (upstaged). SNB in our experience is an accurate method for staging the neck with minimal morbidity in oral cancer patients. Tumor thickness greater than 6mm and the presence of lymphovascular invasion are independent predictors of neck metastases.

S059: HOW MANY NODES ARE NEEDED TO STAGE A NECK? A CRITICAL APPRAISAL

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Introduction: Staging of the neck is an important factor for accurate prognostic and treatment definition of head and neck cancers. Objectives: To assess the importance of nodal yield in staging of oral cancer. Patients and Methods: Patients with primary squamous cell carcinomas of the oral cavity were enrolled in this study. Results: 533 patients were identified that conformed to the inclusion criteria for this report. Neck dissection was performed in all patients. The radical neck dissection accounted for 427 patients (80.1%) and the selective neck dissections for 106 patients (19.9%). Peritumoral vascular infiltration was found in 20 patients (3.8%) and lymphatic embolization in 290 patients (54.4%). Neural infiltration was observed in 204 patients (38.3%). In patients submitted to a radical neck dissection, the number of lymph nodes ranged from 6 to 116 (mean, 45.14 nodes and median, 33.57); while in patients submitted to selective neck dissection the number of nodes ranged from 1 to 87 (mean, 33.57 nodes and median, 32 nodes). For the radical dissection group, the number of positive nodes ranged from 0 to 47 (mean, 1.63 nodes and median, 0 node) and for selective dissection, between 0 and 8 (mean, 0.45 and median, 0 nodes). A significant correlation was found between the number of dissected lymph nodes and the presence of positive nodes in the neck (p=0.001). In patients submitted to a radical neck dissection, it can be described by a second-degree equation. The Y-axis represents the probability of positive nodes and the X-axis, the number of dissected nodes. This equation is Y = -0.016X^2 + 1.959X. The threshold value of the number of nodes that needed to be resected to achieve maximum probability of positive nodes is 61.28. The probability of finding positive nodes was also related to lymphatic invasion (p=0.000), perineural invasion (p=0.000), T stage (p=0.000) and invasion depth (p=0.000). A multinominal logistic regression model was used to identify the effect of these factors upon the probability of node metastasis. The number of dissected nodes (p=0.000), lymphatic embolization (p=0.044) and neural invasion (p=0.030) remained significant. The process was repeated for patients submitted to selective dissection and this analysis was performed by the formula: Y = -0.92X + 1.842X. The threshold was 48.47 nodes. The following factors were found to affect the probability of positive nodes: number of dissected nodes (p=0.000), lymphatic embolization (p=0.000) and gender (p=0.028). In the multinominal logistic regression, the number of dissected nodes (p=0.002) and lymphatic embolization (p=0.001) remained significant.

Discussion: This study demonstrated that the number of retrieved nodes is an important factor in neck staging. The number of lymph nodes yielded may influence the accuracy of the pathological examination and the probability of discovering positive nodes. The use of a curve estimation model allow us to establish the number of dissected nodes that presents the higher probability of positive node finding.

S060: EXTENT OF NECK DISSECTION REQUIRED AFTER CONCURRENT CHEMORADIATION FOR STAGE IV HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Objectives: Concurrent chemotherapy and radiation (CCRT) has improved locoregional control and survival in patients advanced HNSCC. The optimal surgical management of the neck after CCRT remains incompletely defined. We examined outcomes of neck dissection in patients with stage IV (N2A or greater) HNSCC after CCRT. Methods: All patients with N2A or greater neck disease treated at the Cleveland Clinic with primary multimodal CCRT using fluorouracil and cisplatin were retrospectively reviewed. Patient demographics, tumor characteristics, treatment details, and outcomes including regional control, regional recurrence free survival, overall and disease-free survival were compiled. Impact of pretreatment and treatment variables on pathological response and outcomes was assessed. Clinical and pathological nodal involvement was recorded for each neck level both before and after CCRT and neck surgery in order to determine the effectiveness of selective versus comprehensive neck surgery.

Results: Two-hundred fifty patients, treated between 1989-2006, met the criteria for review. Of these, 241 achieved initial primary site control following CRT, and were therefore appropriate for analysis. The analyzed cohort consists of the 141 patients who underwent a total of 161 neck dissections. No residual cancer was found in 116 necks and this was considered a pathologic complete response (pCR). Residual tumor, a pathologic partial response (pPR) was found in 45 necks, and no patient experienced disease progression in the neck after CCRT. pCR was less common in patients with moderate tumor differentiation (as opposed to poor or well differentiated tumors; p=0.03) and, there was a statistical trend suggesting less frequent pCR in those with more advanced T stage of primary tumor (p=0.07). Regional recurrence (RR) in patients after CCRT and neck dissection occurred in 10 patients, and in five who did not undergo neck dissection. Neck recurrence was more frequent in patients with pPR vs. pCR (p=0.008) and in patients experiencing a primary site recurrence. Among the 43 neck dissections in which residual disease was found, 36 (86%) were pathologically positive in the originally positive nodal levels. Seven specimens were positive outside the original nodal levels, but within one level of original disease. Only one neck dissections (2.2%) were positive at more distant neck node levels. Fifty-six percent of patients with RR were found to have synchronous recurrence at the primary site. RR was not more common in patients undergoing a "superselective" neck dissection (defined as removal of one to two nodal levels) as opposed to LRND, RND, or SND. Overall survival, time to regional recurrence, and disease-free survival were not improved by neck dissection but may have been confounded by the fact that neck surgery was performed more often in cases with more advanced regional disease.

Conclusions: This review suggests that a selective neck dissection for stage IV squamous cell carcinoma following CCRT is oncologically sound if the original nodal levels plus one distal level is removed. Regional recurrence following CRT should always prompt reexamination of the primary site as it is frequently associated with local recurrence.

S061: INCIDENCE OF REGIONAL RECURRENCES AFTER (CHEMO)RADIOTHERAPY FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Objectives: Many locoregionally advanced head and neck squamous cell carcinoma (HNSCC) patients are now treated with radiation, with or without concurrent chemotherapy, to achieve organ preservation. The management of nodal disease postradiation is controversial. The purpose of this study was to evaluate the incidence and localization of regional recurrences after primary (chemo)radiotherapy for HNSCC without standard neck dissection. Methods: From May 1987 to January 2007, 330 patients with HNSCC were treated to 66-72 Gy in 6-7 weeks, with (32.1%) or without (67.9%) concomitant chemotherapy (cisplatin 100 mg/m2 every 3 weeks. The majority of patients had locally > T2: 67.5%) and/or regionally (N1: 19.1%; N2: 51.5%; N3: 6.1%) advanced disease. No planned neck dissections were performed. Data on clinical outcome were retrospectively collected; location of the original nodal disease and region-
al recurrence was indicated on imaging and correlated with radiation dose. Results: Median follow-up was 42.4 months for patients still alive at the close-out date. Five-year overall and disease-specific survival was 41% and 51%, respectively. Loco-regional, local, regional and distant control was 53%, 60%, 83% and 78%, respectively. Thirty-nine patients (11.8%) relapsed in the neck, but only 16 patients (4.8%) developed an isolated regional recurrence. In 6 patients the recurrence was due to persistent nodal disease after radiation, while in 10 patients it was a true recurrence after a median of 17 months since treatment (range: 11 - 32 months). Of these 16 patients with isolated neck disease, 9 patients could be successfully salvaged by surgery (n = 7) or radiotherapy (n = 2) and remained disease-free at a median 14 months (range: 3 - 33 months) after recurrence. Only 2 patients (0.6%) developed an isolated recurrence in the electively treated nodal levels. Twenty patients (6.1%) relapsed locally as well as regionally, 3 of whom could be successfully salvaged by surgery. Three patients (0.9%) failed in the neck and at a distant site, without local recurrence, at 8, 9 and 13 months after treatment. Conclusion: Isolated nodal recurrences are uncommon and recurrences in the electively treated neck are extremely uncommon. Both can be treated successfully with salvage surgery.

SO62: SELECTIVE VERSUS COMPREHENSIVE NECK DISSECTION AFTER CHEMORADIATION FOR ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Introduction: A planned post-primary chemoradiation treatment (CRT) neck dissection for squamous cell carcinoma of the head and neck (SCCHN) is often considered for patients with N2 or greater neck disease. However, it remains unclear whether a comprehensive neck dissection (CND) including levels IV-V is necessary or whether a selective neck dissection (SND), defined as anything less than levels IV-V, is sufficient. The objective of this study was to investigate the outcomes of planned CND and SND in a cohort of patients undergoing a uniform CRT regimen. Methods: Medical records of all patients treated with primary CRT and post-CRT neck dissection for locoregionally advanced SCCHN at Greater Baltimore Medical Center were reviewed between 2001 and 2007. All patients received 7000 cGy and 6000 cGy external beam hyperfractionated radiation therapy to primary disease sites and involved cervical lymphatics respectively, with concomitant cisplatin (60 mg/m2) and 5-FU (3000 mg/m2) given weeks 1 and 6. Outcome parameters analyzed for each patient included pre- and post-CRT primary and neck stage, location of positive nodes by clinical, radiographic, and pathologic exam, type of neck dissection(s) performed, pathologic status of the neck dissection specimen, surgical complications, length of follow-up, length of survival, and disease-free survival. Results: In 101 patients, 54 patients (54%) received CND or SND groups and survival outcomes were not significantly different. The high rate of residual disease demonstrated in this study supports the need for post-CRT neck dissection. While complication rates were not significantly different between the two groups, the rate of surgical complications was higher in the SND group. Conclusion: SND is an appropriate surgical approach in patients with advanced nodal disease to identify the subset of patients who would benefit from planned neck dissection from those who will not. Methods: 29 patients with clinical neck disease staged as N2 have been enrolled in the study. All patients were treated with radical chemoradiotherapy. After 12 weeks 21 patients were evaluated with neck US, MRI and PET. Regardless of clinical and radiological response all patients were underwent neck dissection. The remaining 8 patients are currently waiting for completion of the imaging evaluation and are not included in the study. Results: The histopathological node status of each patient were compared to imaging findings (US, MRI and PET) to determine the specificity, sensitivity and diagnostic accuracy of each radiological technique. The sensitivity, specificity and diagnostic accuracy of neck US were 90%, 72.7% and 81% respectively. The sensitivity, specificity and diagnostic accuracy of MRI were 80%, 54.5%, and 66.7% respectively. The sensitivity, specificity and diagnostic accuracy of PET were 40%, 90.0%, and 66.7% respectively. Conclusion: Our preliminary results indicate that PET performed 12 weeks after chemoradiation therapy has the highest specificity in the detection of residual disease. Neck US has the highest sensitivity with the best negative predictive value. MRI has high sensitivity but a low specificity. Based on this preliminary analysis we suggest that patient with no clinical residual disease in the neck and negative MRI, US and PET 12 weeks after definitive chemoradiation therapy are highly reliable for the absence of residual cervical nodal disease and can be safely observed avoiding neck dissection and its complications. In patients with clinical residual nodal disease in the neck and metabolically inactive radiological pattern (negative PET, no contrast enhancement and low signal in T2 and fat suppressed sequences at MRI and no vascularization at US) 12 weeks after chemoradiation therapy selective neck dissection is feasible. In patients with positive PET, neck US or MRI a planned modified or radical neck dissection is advisable.

SO63: PLANNED NECK DISSECTION AFTER CHEMORADIO- THERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER: ROLE OF NECK US, MRI AND PET

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Objective: The role of planned neck dissection after chemoradiation therapy for locally advanced head and neck cancer is evolving. Routine planned neck dissection adds significant morbidity to treatment and should ideally be avoided in those patients in whom surgery is either unnecessary (no residual tumor). Recent data suggest that a percentage of patients with extensive (N2-N3) neck disease who demonstrate a complete response to chemoradiation therapy may harbor residual occult metastases, and identification of this subset of patients remains a clinical challenge. The purpose of this prospective study was to determine the ability of neck ultrasonography (US), magnetic resonance image (MRI) and positron emission tomography (PET) in detecting residual cervical metastases after chemoradiation therapy in patients with advanced nodal disease to identify the subset of patients who would benefit of planned neck dissection from those who will not. Methods: 29 patients with clinical neck disease staged as N2 have been enrolled in the study. All patients were treated with radical chemoradiotherapy. After 12 weeks 21 patients were evaluated with neck US, MRI and PET. Regardless of clinical and radiological response all patients were underwent neck dissection. The remaining 8 patients are currently waiting for completion of the imaging evaluation and are not included in the study. Results: The histopathological node status of each patient were compared to imaging findings (US, MRI and PET) to determine the specificity, sensitivity and diagnostic accuracy of each radiological technique. The sensitivity, specificity and diagnostic accuracy of neck US were 90%, 72.7% and 81% respectively. The sensitivity, specificity and diagnostic accuracy of MRI were 80%, 54.5%, and 66.7% respectively. The sensitivity, specificity and diagnostic accuracy of PET were 40%, 90.0%, and 66.7% respectively. Conclusion: Our preliminary results indicate that PET performed 12 weeks after chemoradiation therapy has the highest specificity in the detection of residual disease. Neck US has the highest sensitivity with the best negative predictive value. MRI has high sensitivity but a low specificity. Based on this preliminary analysis we suggest that patients with no clinical residual disease in the neck and negative MRI, US and PET 12 weeks after definitive chemoradiation therapy are highly reliable for the absence of residual cervical nodal disease and can be safely observed avoiding neck dissection and its complications. In patients with clinical residual nodal disease in the neck and metabolically inactive radiological pattern (negative PET, no contrast enhancement and low signal in T2 and fat suppressed sequences at MRI and no vascularization at US) 12 weeks after chemoradiation therapy selective neck dissection is feasible. In patients with positive PET, neck US or MRI a planned modified or radical neck dissection is advisable.
S065: PAROTIDECTOMY: 17 YEAR INSTITUTIONAL EXPERIENCE

Background: Parotidectomy is performed for a variety of indications including benign and malignant primary tumors of the parotid gland, metastatic disease to the gland, and chronic sialoadenitis. This study explores the parotidectomy experience at our institution during the past 17 years. Methods: A retrospective review of all parotidectomies performed at Dartmouth Hitchcock Medical Center from 1990 to 2007 was performed. Results of variables including patient demographics, histopathologic information, initial presentation, use of fine needle aspiration, surgical procedures performed, final pathology, complications, and survival for primary malignant tumors. Results: 341 parotidectomies were performed on 340 patients. Age at time of surgery ranged from 3 years to 91 years with average age of 57 years. The most common presenting complaint was painless mass with or without enlargement in 62% of cases (210/341). Fine needle aspiration was performed in 94 patients (28%). Fine needle aspiration correctly identified the underlying pathology in 65% of cases (210/341). There were 232 superficial parotidectomies and 98 total parotidectomies performed. Additional procedures included neck dissection (36), temporal bone resection (11), and flap (rotation, pedicled, free) reconstruction (71). Of the 341 parotidectomies 7% (25/341) were for chronic sialoadenitis, 8% were part of a combined procedure, 278 (82%) were for tumor. Of the tumors excised 67% (186/278) were benign, the most common being pleomorphic adenoma (61%, 114/186). Malignant tumors constituted 27% of tumors, the most common being metastatic squamous cell carcinoma from a cutaneous source (37%, 34/92). Mucoepidermoid carcinoma was the most common primary malignant tumor (12%, 11% of all tumors). The most common complication was infection in 67% (54/81), while 65% of cases of facial weakness associated with surgery for malignant pathology. Other complications included seroma (6.5%), abscess (3%), and hematoma (2%). Follow up ranged from 0 to 120 months, average 23 months. Conclusions: In this study we present our institutional experience with parotid surgery over the past 17 years. The pathologic findings in this study are consistent with those reported in the literature. Complication rates in general are low and more commonly associated with surgery for malignant tumors.

S066: PROGNOSTIC FACTORS IN MINOR SALIVARY GLAND CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX

Introduction: Minor salivary gland carcinomas (MSGC) of the oral cavity and oropharynx are infrequent malignancies of the head and neck area. Few studies exist at present that describe experience with these tumors. The aim of this study is to define prognostic factors and to describe the biologic behavior and management guidelines of oral cavity and oropharynx MSGC. Methods: Retrospective study of clinical records of patients with MSGC of the oral cavity and oropharynx, confirmed by histopathology study, presenting to a tertiary referral cancer center in the period from January 1990 to December 2005. Patients included underwent treatment with curative intent either with surgery, radiation therapy, or a combination of both. Staging was performed according to the 2002 American Joint Committee on Cancer (AJCC) criteria. Survival analyses was performed with the Kaplan-Meier and log-rank test. Multivariate analyses of prognostic factors were performed using the Cox method. Results: Seventy-six patients were evaluated, including 32 women (42.1%) and 44 men (57.9%). Their mean age was 49.8 years (16.6 SD). Mean follow-up time was 4.6 years (range 0.85-13.7 years). The most commonly affected site was the hard palate in 30 patients (39.4%), followed by the soft palate 9 cases (11.8%), retromolar trigone 8 (10.5%) and floor of the mouth 7 cases (9.2%). Ten cases (13.1%) were T1, 25 cases (32.8%) were T2. T3 and T4 were found in 10 (13.1%) and 31 (40.7%) cases, respectively. Forty-five patients (59.2%) had ipsilateral neck disease and 17 (22.8%) had distant metastases. Most common histology was adenoid cystic carcinoma in 35 (45%) cases, followed by mucoepidermoid carcinoma in 22 (29%) patients. Eighteen (23.7%) patients underwent surgery alone, 36 (47.5%) combined surgery and radiation therapy, and 22 (28.9%) received radiation therapy alone as treatment for their primary disease. Local recurrence occurred in 11 cases (14.5%), regional recurrences in five (6.6%), bone metastases in one (1.3%) patient, and 10 (13.2%) patients had lung metastases. Mean disease-free survival was 10.5 years (95% CI 8.9-12). Median disease-specific survival was 6.55 years. Factors associated to disease-free survival according to univariate analyses were: T and N classifications, histology, tumor size, surgical margins, hemoglobin and albumin levels and treatment modality. Multivariate analysis demonstrated that only tumor size and tumor histology were significant factors associated to disease-free and to disease-specific survival. Conclusion: Oral cavity and oropharyngeal MSGC present with advanced stage. Significant prognostic factors for disease-free survival were tumor size and histology in the multivariate analyses. Tumor size as categorized in our study is a better predictor for recurrence than T stage. We suggest reevaluation of the T, N, M staging system for MSGC.

S067: PROGNOSTIC ROLE OF EPIDERMAL GROWTH FACTOR RECEPTORS 1 & 2, ANDRONEGON RECEPTOR AND KIT IN 111 SALIVARY GLAND CANCER

Background: We report the expression pattern and the role of EGFR, HER2, KIT and AR in 111 cases of salivary gland cancer. Methods: Surgical specimens were retrospectively analyzed. Formalin-fixed paraffin embedded sections from all 111 cases were collected, and the expression of EGFR, HER2, AR and KIT was assessed by immunohistochemistry (IHC). Fluorescence in situ hybridization (FISH) was also performed in all HER2 2+ cases. Overall (OS) and relapse free survival (RFS) were estimated to evaluate the prognostic role of receptor expression in the entire series, and a subgroup analysis was also performed to assess the prognostic role of KIT expression in adenoid cystic carcinoma (ACC), HER2 and AR expression in salivary duct cancer (SDC) and adenocarcinoma, respectively. A multivariate analysis is ongoing to examine other prognostic factors such as the site of primary tumor (major versus minor salivary gland), stage, macroscopic (R0) or microscopic (R1) residual disease and the perineural involvement. Results: There were 47 (42%) ACC, 21 (19%) SDC, 17 (15%) adenocarcinoma. There were 26 patients (23%) with other histotypes, among which 6 high grade mucoepidermoid and 5 myoepithelial cancers. Stage according to AJCC VI edition was III in 27 (24%) cases and IV in 65 (59%) cases, not evaluable in 19 (17%). EGFR was the most expressed marker, being present in 60 (54%) cases. KIT positive cases were 43 (39%), mainly in ACC samples (35/43, 81%); HER2 2+ cases were 13 (12%); 8 out of 13 (61%) were SDC. Ten out of 13 (77%) cases were also FISH positive. AR was present in 12 (11%) cases, 8 of them were SDC (67%). On the entire series, preliminary results show no prognostic role in terms of RFS and OS for EGFR, HER2 and AR, with a favorable trend for OS in KIT+ cases. Apparently, the impact of KIT+ on OS was largely due to ACC patients (p=0.61). Likewise, there was a favourable trend of AR expression in terms of OS (p=0.099) in SDC and adenocarcinoma. Conclusions: This preliminary analysis suggests that EGFR, HER2, KIT and AR are expressed differently in the various histotypes. KIT expression seems to be the most favorable prognosticator for OS, and its overexpression seems to correlate with a better OS in SDC and adenocarcinoma.

S068: EXPRESSION OF EPIDERMAL GROWTH FACTOR FAMILY OF RECEPTORS BY COMPARATIVE METHODS IN SALIVARY DUCT CARCINOMAS

Objective: Salivary duct carcinoma, a high-grade adenocarcinoma morphologically similar to mammary carcinoma, also manifests overexpression...
of epidermal growth factor family of receptors, EGFR and HER-2. Limited information is available regarding the mechanisms and the exclusivity of over-expression in these tumors. As these markers may have both therapeutic and prognostic significance, correlative studies to define which methods provide optimal assessment are needed. We therefore evaluated both markers in salivary duct carcinomas by several techniques to determine the complementarity of the results in assessing the biological roles of these factors. Methods: Tissue microarrays were generated using tissue obtained primarily from the Department of Pathology database. A tissue microarray was created from these blocks and used to analyze tumors for immunohistochemical expression of EGFR and HER-2. Immunohistochemistry (IHC) studies were evaluated for membranous expression of tumor cells; 3+ = strong complete in > 30%; 2+ = weak complete >30%; 1+ = partial membranous staining; 0 = negative or <30% staining. In addition, EGFR and HER-2 gene copy number and ploidy status of chromosomes 7 and 17 centromeres by fluorescence in situ hybridization (FISH) were performed on the tissue microarray. In 11 tumors, the DNA copy number was also evaluated by RT-PCR using taqman method and sequencing exons 18, 19, and 21 of the EGFR gene for mutations was performed. Groups were compared by Fisher's exact test. Results: Seventeen (25.8%) of 66 tumors showed membranous HER-2 staining (10+; 3+; 2+; 4+). Eight of these were HER-2 gene amplified by FISH (7+; 3+; and 1+ HER-2 expression by IHC (p<0.0001). RT-PCR showed increased DNA copy number in 1 of 3 HER-2 amplified tumors by FISH. Chromosome 17 hyperploidy (average >2.5 copies per cell) was present in 9 (17.6%) of 51 tumors; of these 2 were immunohistochemically reactive (1+; 3+; 2+; and 1+). Eight of these were amplified by FISH (7+; 3+; and 1+ HER-2 expression by IHC (p<0.0001). RT-PCR showed increased DNA copy number in 1 of 3 HER-2 amplified tumors by FISH. Chromosome 7 hyperploidy was present in 14 (23.3%) of 60 tumors; of these 11 were immunohistochemically reactive (9+; 3+; and 1+; 2+; and 0). Ploidy of chromosome 7 correlated with immunohistochemical expression +3 vs <-2 (p=0.02). Hyperploidy of chromosome 7 (EGFR chromosome) also correlated with increased risk of lymph node metastases (p=0.03) and persistent disease or death (p=0.03). All patients alive without disease were negative for chromosome 7 ploidy. No correlations were noted in ploidy of chromosome 17, gene amplification, age or sex. Conclusions: Our results show that in salivary duct carcinoma: 1) HER-2 over-expression by IHC is frequently correlated with HER-2 gene amplification, 2) IHC for HER-2 can screen for the subset of patients who may benefit from trastuzumab therapy, 3) High EGFR expression by IHC is frequently associated with chromosomal ploidy and not gene amplification, 4) Further analysis to address other mechanisms of EGFR over-expression is needed.

S069: THE ROLE OF RADIOThERAPY IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK

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Objectives: Adenoid cystic carcinoma represents 3% of head and neck malignancies, and may recur locally and with distant metastases many years after diagnosis. Until recently, surgery alone was preferred, with post-operative radiotherapy reserved for locally advanced or recurrent cases. More recently, radiotherapy has been used extensively. This series reviews the impact of an evolving treatment paradigm over the last 40 years at the University of Iowa Hospitals and Clinics. Methods: Charts were retrospectively reviewed from the Department of Pathology database. A subset were prospectively accrued through the Iowa Quality of Life and Outcomes dataset. Analysis was directed to compare surgery alone with surgery and post-operative radiotherapy. The last 40 years at the University of Iowa Hospitals and Clinics. Survival following local recurrence (N=67) was significantly improved by: any treatment compared with none (55.1% vs. 0% at 5 years p=0.004); surgery compared with non-surgical treatment (61.9% vs. 10.5% at 5 years p=0.006). Radiotherapy did not significantly improve for local recurrence (53.3% vs. 32.4% at 5 years p=0.139). For those with distant metastases, chemotherapy did not significantly increase survival (p=0.795) with the addition of post-operative radiotherapy to surgery alone. Survival following local recurrence (N=67) was significantly improved by: any treatment compared with none (55.1% vs. 0% at 5 years p=0.004); surgery compared with non-surgical treatment (61.9% vs. 10.5% at 5 years p=0.006). Radiotherapy did not significantly improve for local recurrence (53.3% vs. 32.4% at 5 years p=0.139). For those with distant metastases, chemotherapy did not significantly increase survival (p=0.795) with the addition of post-operative radiotherapy to surgery alone.
OUTCOMES: PALLIATIVE/SUPPORTIVE CARE/REHABILITATION

5073: TUBE FEEDING IN HEAD AND NECK CANCER PATIENTS RECEIVING CONCOMITANT CHEMORADIOThERAPY J.T. Chang 1, L.Chen 1, E.Y.Chen 1, K.Fan 2, S.Huang 1, C.Lin 1, I.Chen 2, C.Liao 1, H.Wang 1, Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China; 2Chang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China

Introduction: To evaluate the impact of tube feeding timing for head and neck cancer patients receiving concomitant chemoradiotherapy (CCRT).

Material and Methods: Two hundred and eight consecutive high risk head and neck cancer patients received CCRT. The median age was 51.5. Fifty-one (24.5%) patients received postoperative adjuvant therapy. The stage distribution was stage II: 50 (24%), III: 41 (20%) and IV: 117 (56%). The tumor site distribution was nasopharynx: 81 (39%), oral cavity: 72 (35%), hypopharynx: 28 (13%), oropharynx: 19 (9%) and larynx: 8 (4%). The radiotherapy was 46 Gy to subclinical disease area and 66 Gy for tumor bed and 72-76 Gy for gross disease. The chemotherapy used was weekly CDPD and oral 5-FU analogue. FACT-H&N 4th version questionnaire was used to assess the patients’ health related quality of life (HRQoL) and 5 points pain score for general pain assessment weekly during the radiotherapy and monthly after radiotherapy. Electrolyte tube (ET) feeding was performed by fluoroscopy guided percutaneous gastrostomy. Therapeutic tube (TT) feeding was performed by nasogastric tube or gastrostomy tube.

Results: Twenty-four patients received ET feeding, 77 patients received TT feeding and 107 patients had no tube (NT) feeding. There were significant body weight (BW) change among these three groups, BW loss [initial BW: lowest BW]/initial BW was 6.0 +/- 4.5%, 8.2 +/- 5.3%, 9.3 +/- 5.6 and BW change [initial BW: BW at 3 months after radiotherapy]/initial BW was 4.9 +/- 5.8%, 6.0 +/- 6.8%, 7.7 +/- 6.5% in ET, TT and NT patients. However, ET and TT patients experienced more severe pain than NT patients. There were no significant difference in HRQoL, chance of completed planned radiotherapy and total radiotherapy duration among three groups. Patients experienced more severe pain had significant worse HRQoL.

Conclusion: There are less body weight loss for H & N cancer patients received ET feeding for CCRT compared to TT and NT patients. However ET feeding will let patients experience more pain but similar HRQoL and chance to complete of planned treatment. ET feeding may not be necessary considered as routine for H & N patients received CCRT. Aggressive pain management may be important to improve the patients’ HRQoL during CCRT.

5074: DOES NECK DISSECTION AFTER CHEMORADIATION THERAPY FOR OROPHARYNGEAL CARCINOMA AFFECT SWALLOWING FUNCTION? A.G. Sacco 1, D.B. Chepeha 1, T. Lyden 1, M. Haxer 1, F. Feng 1, S. Scheckman 1, F.P. Wordon 1, D. Normolle 1, A. Eisbruch 1, U. Cancer Team 1, University of Michigan, Ann Arbor, MI

Objective: To determine the effect of neck dissection on swallowing in patients who have undergone chemoradiation therapy. Methods: A phase II clinical trial of concurrent IMRT and weekly carboplatin with paclitaxel was conducted to determine swallowing function and response rate. Patients were eligible if they were previously untreated, presented with stage III/IV oropharyngeal squamous cell carcinoma, and underwent definitive therapy with IMRT aiming at the sparing of the major salivary glands, superior constrictor and the larynx. 74 patients were enrolled and 21 underwent a post-treatment neck dissection. Of the 21 patients, 15 underwent selective neck dissection levels I-V, 2 selective neck dissection levels II-III, 3 modified radical neck dissection and 2 radical neck dissection.

Conclusion: There was no significant difference in HRQoL, chance of completed planned radiotherapy and total radiotherapy duration among three groups. Patients experienced more severe pain had significant worse HRQoL.

Conclusion: There are less body weight loss for H & N cancer patients received ET feeding for CCRT compared to TT and NT patients. However ET feeding will let patients experience more pain but similar HRQoL and chance to complete of planned treatment. ET feeding may not be necessary considered as routine for H & N patients received CCRT. Aggressive pain management may be important to improve the patients’ HRQoL during CCRT.
Comparisons made
Patients with advanced stage head and neck cancer often
Laryngeal elevation assessed post-chemoradiation, but prior to neck dissection, was com-
tained compared to the average of all values post neck dissection, up to 24 months.
Laryngeal elevation averaged 0.34 seconds longer post neck dissection (p<0.003). In contrast, patients who did not undergo neck dissection short-
tened their laryngeal elevation scores by an average of 0.07±0.11 seconds (p=0.51), indicating no clinical deterioration. This suggests that dissec-
ton of the larynx affects the elevation of the larynx. The larynx is a voluntary muscle, and is associated with longer laryngeal elevation scores. Longer laryngeal elevation scores could not be correlated with subjective scores of swallow-
ing function. At the 12 month interval, patients’ self report of swallowing on the UM-HNQOL and the UW-QOL showed no statistical difference from baseline. In each of the questions, on a Likert scale of 1-5, patients’ mean response was consistently scored one category below a perfect score of 5/5 except for “swallowing liquids” which patients scored 5/5.
Conclusion: Neck dissection after chemoradiation therapy in patients with oropharyngeal squamous carcinoma increases laryngeal elevation time. This finding should adversely affect swallowing function but no subjective measure could be correlated, which was likely due to the good overall patient-reported outcomes.

S075: PROSPECTIVE FUNCTIONAL STUDY IN PATIENTS WITH HEAD AND NECK CANCER AFTER TREATMENT WITH CHEMOTHERAPY AND RADIOTHERAPY

Background: Simultaneous chemotherapy and radiotherapy (CT+RT) are widely used to treat head and neck cancer patients (HN) with advanced disease and for organ preservation. Sometimes the latter is not accompanied by the preservation of the function. Objectives: To know the incidence of functional abnormalities as dysphagia and aspiration in patients treated with CT+RT for HN. Materials and Methods: Seventy two patients (54 male and 18 female), median age 58 years with HN treated with CT+RT and disease free for at least six months were evaluated. Patients were divid-
ed in four groups according to disease free time: group1 6 to 11 months (23 pts), group2: 12 to 23 months (27 pts), group 3: 24 to 59 months (10 pts) and group 4: 60 to 120 months (12 pts). The primary sites were oropharynx: 36 pts, larynx: 23 pts, nasopharynx: 8 pts, hypopharynx: 4 pts and oral cavity: 1 pt. The swallowing performance scale of Kanell and the Performance scale for usual functions of the University of Chicago were used. In addition a clinical evaluation of the swallowing act was performed using liquid, semisolid and solid food and a video fluoroscopy. The items evaluated were speech understanding, eating in public, normalcy of diet, presence of tracheotomy, presence of aspiration according to primary site, type of aspiration and way of feeding after treatment. Results: 97% (70/72) of patients presented with some kind of dysfunction 38/70 (54%) presented with aspiration and in 14 patients (36%) this was silent. Aspiration was more frequent in patients with a primary located in the oropharynx: 24/36 (66%) than in other sites: Larynx: 9/23 (39%), Nasopharynx: 3/8 (37%), Hypopharynx: 1/4(25%). However after rehabili-
tation which consisted of diet modifications and postural strategies only 4% (3/70 patients) needed enteral complementary diet and 7% (5/70) exclusive enteral diet. 29/70 patients (41%) had dysphagia only for solids and they only needed diet modifications. 8/72 (11%) required a perma-
tent tracheotomy at the time of evaluation. Speech was always understand-
able in 57% of pts in group 1, 44% en group 2, 70% in group 3 and 58% in group 4. Conclusions: 1) Prevalence of dysphagia was very high. This is important in order to inform the patients of the risk of dysfunction after treatment. 2) Patients’ perception of their swallowing skill may not match the real one, so it must be directly assessed by objective tests. 3) Response of swallowing function after rehabilitation with postural strategies was very high.

S076: SWALLOWING FUNCTION FOLLOWING RADIONUROThERAPY OR CHEMORADIOTHERAPY FOR ADVANCED STAGE HEAD AND NECK CANCER

Introduction: Patients with advanced stage head and neck cancer often require combined modality therapy to optimize disease control. In the past, this usually consisted of surgery and postoperative radiotherapy. More recently, combinations of chemotherapy and radiotherapy have increasingly been utilized in an attempt to avoid the anatomic loss and associated morbidity of extensive surgical resection. Such non-surgical treatment strate-
gies are intended to preserve essential speech and swallowing function without compromising oncologic outcome. Objectives: To assess swallow-
ing function following radiotherapy or combined chemotherapy and radio-
therapy for advanced stage head and neck cancer using gastrostomy tube (G-tube) dependence as a measure of outcome. Methods: A retrospective single institution cohort study including all patients who received radiotherapy (RT) or combined chemotherapy (CT) and radiotherapy as primary treatment for stage II, III, and IV cancer from 2002 through 2006. Only patients followed for a minimum of 6 months were eli-
gible for analysis. Patients who underwent resection of their primary tumor were excluded. Outcome was assessed using a three point scale: complete-
gly G-tube dependant; partial oral diet with G-tube supplementation; and oral intake only. Results: A total of 29 patients met the inclusion criteria during the study period. There were 9 patients with stage 3 disease and 20 patients with stage 4 disease. Cimetaion CT and RT was utilized in 25 of 29 patients (18 patients received induction CT plus concurrent CT and RT; 7 patients received concurrent CT and RT only). Fifteen of the 29 patients received intensity-modulated radiotherapy (IMRT). The rates of total and partial G-tube dependence were 35% and 38% respectively at 2 months post-treatment, but decreased to 17% and 21% at 6 month follow-up. There was more gradual improvement at one year and beyond, with 10% of the study population totally G-tube dependent and an additional 10% requiring some supplemental G-tube feeding at last follow-up. There was a trend towards a better swallowing outcome in patients with stage 3 disease, oropharyngeal primary sites, and in those patients who received IMRT. Conclusion: This study demonstrates that patients experiencing significant short-term swallowing dysfunction experience significant improvement with RT or CT and RT for advanced stage head and neck cancer. Swallowing function improved significantly at 6 months post-treatment and showed some further improvement at 1 year post-treatment and beyond, however at last follow-up 10% of our study group was totally G-tube dependant, and an additional 10% still required some supplemental G-tube feeding. Our study demonstrated a trend towards better swallowing outcome in patients treated with IMRT, which suggests this technical advance in radiotherapy may result in decreased morbidity in this patient population.
for tube care, or complications. 6 patients (12%) were inadequately assessed for method of insertion, and 33 (66%) received no prophylactic antibiotics prior to placement. Pre and post treatment dietetic clinics provided a closed loop for insertion and removal of feeding tubes. Gastroenterology and radiology expertise consolidated patient selection criteria, suitability for method of insertion and post placement care. 2nd limb analysis data reflected 50 patients (100%) received gastrostomy counselling by the dietitian at pre-treatment, no hospital admission for nutritional management, and ongoing monitoring in the post treatment clinic for dietary rehabilitation facilitating tube removal. 48 patients (96%) had overnight stay post placement, 7 (2%) extending to 3 days and 12 (2%) 30 days due to complications. 10 patients (20%) screened by gastroenterology prevented radiological placement in 2 (4%). All patients received prophylactic antibiotics. Conclusion: Specialist dietitians implemented timely nutrition support, gastrostomy counselling and rehabilitation in dietetic clinics. Effective patient education supporting consent process, and preventing tube dependency. Dietetic led specialist care pathway improved screening and intervention, reduced complications and hospital admissions. Resulting in cost savings, efficient prophylactic gastrostomy placement, and evidence for dietitian’s role to promote functional and patient centred outcomes.

S078: PARENTRAL VS ENTERAL NUTRITION AFTER MAJOR NECK SURGERIES: IS THERE A DIFFERENCE IN OUTCOMES OR COMPLICATIONS? M.M.Abu-Samra1, N.El-Bahnasawy1, N.M.Rizk1,2, M.A.Khalil1, M.R.Khalil1, M.T. El-Bayoumy1, H.Elsheikh1,1Mansoura University, Mansoura Egypt; 2University of Alberta, Edmonton, AB, Canada

Objective: To determine which method of feeding (enteral or parental) after head and neck surgery has superior outcomes with regards to: 1) Postoperative complications, 2) Length of hospital stay, 3) Wound healing, 4) Resumption of oral feeding. Methods: A prospective randomized controlled trial was conducted from January 2003 to January 2006. All patients undergoing major head and neck surgery were eligible. Patients with severe metabolic disorders (as uncontrolled diabetes, renal insufficiency, hepatic decompensation) and patients with cardiac disease were excluded. 40 patients were randomized to receive either enteral nutrition (20 patients NGT) or parental nutrition (20 patients TPN). The patients were monitored for postoperative complications, wound healing, hospital stay, start of oral feeding and weight loss. All patients in the TPN group had a central venous catheter inserted at time of surgery. Nutrition was started 24 hours post-operative in both groups. All patients had tracheotomy. All patients in both groups received antibiotic prophylaxis until oral feeding was resumed. Statistical analysis was done using the statistical package for social sciences version 10.0 (SPSS @; 10.0, Chicago, IL). Results: The study included 36 males and 4 females, with ages range from 42 to 71 years. Both groups were matched with regards to disease site, stage, and demographics. The mean duration of nutrition was 9.65, 9 days for TPN and 11.9 days for NGT group respectively. The mean hospital stay was: 11.65 days in TPN group and 11.9 days for NGT group. Wound dehiscence and infection was in 15% in TPN and 20% NGT. Weight loss was 2.6 K gm for TPN group and 2.39 K gm for NGT group. None of these comparisons were statistically significant. There were no major postoperative complications in either group. Conclusion: There is no difference in the postoperative outcomes when either parental or enteral nutrition is used after major head and neck surgery.

S079: THE IMPACT OF PHARYNGEOESOPHAGEAL STRICTURES IN THE HEAD AND NECK CANCER PATIENT B.P. Messing,1 The Greater Baltimore Medical Center, Baltimore, MD

Objective: Organ preservation protocols using concurrent chemotherapy and radiation therapy result in increased toxicities including the formation of edema, scarring and pharyngoesophageal strictures. Palatal and pharyngeal constrictor muscles, oral cavity, oropharyngeal mucosa, tongue base, epiglottis, and cartilaginous larynx may all receive doses that lead to restrictive fibrosis and long-term scarring resulting in stenosis of the upper digestive tract. Specific changes in swallowing function are experienced early and very often become chronic and debilitating for the patient. Our objective was to review our single institution experience in patients with pharyngoesophageal strictures after organ preservation therapy. Methods: A retrospective chart review of 108 patients who had undergone uniform concurrent chemotherapy and hyperfractionated radiation treatment for locally advanced head and neck cancer (stage 3 or 4) between 2000 and 2007 was performed. Prophylactic percutaneous gastrostomy tubes were inserted in all patients to ensure adequate nutrition and hydration during and post treatment because of known changes in swallow function. Results: Post treatment, patients attempted to resume oral intake, which is a known slow and arduous process. On post treatment follow up visits patients complained of difficulty swallowing, extended time to eat, regurgitation of food and liquids to a more severe case in which the patient was unable to swallow her own saliva. Modified Barium Swallow were performed and a pharyngoesophageal narrowing or stricture was identified. Post treatment course was complicated by esophageal strictures in 9% (10/108) of this cohort of patients, placing them at risk for aspiration and nutritional compromise. Primary site was 9 oropharynx and 1 hypopharynx (6 tonsil, 3 base of tongue, 1 posterior pharyngeal wall). The time post treatment for diagnosis of the pharyngoesophageal stricture was on average 6.5 months (range 2.19 months post treatment). Patients required on average 2.4 esophageal dilation procedures. Swallow function was improved significantly in 9 of the 10 patients with single or serial esophageal dilations and intensive swallow therapy for treatment other oropharyngeal deficits. Conclusions: Early identification, long-term follow up and management of pharyngoesophageal strictures are necessary to achieve optimal swallow function, reduce the risk of aspiration and enable patients to return to safe oral intake. Achieving this requires close patient monitoring and functional defects and complications using a collaborative approach between head and neck surgery, radiation and medical oncology and speech pathology swallowing specialists.

S080: LONG-TERM RESULTS OF PROVOX ACTIVALVE FOR EARLY LEAKAGE IN LARYNGECTOMY PATIENTS J.Soolsma1, M.W.van den Brekel1, A.H.Annemiek1, F.J.Hilgers1,1Netherlands Cancer Institute, Amsterdam, The Netherlands

Objective: To assess long-term results of a prosthesis for voice rehabilitation after total laryngectomy (Provox ActiValve) aiming at solution of frequent Candida- and underpressure-related replacements. Methods: Retrospective assessment of device lifetime, indications for replacement, voice quality, and maintenance issues, measured by a structured trial specific questionnaire, in a cohort of 42 laryngectomized patients, experiencing a short Provox2 device lifetime before the use of the ActiValve (median 2 days). Results: Median device-related lifetime of Provox ActiValve, replaced for leakage through the device and those still in situ at the date of data collection (N=32), was 337 days (mean 376 days): a statistically significant 16-fold increase compared to Provox2 (P<0.001). In 10 patients replacement was fistula-related (median after 86 days): esophageal pouch (N=4), fistula granulation (N=3), extrusion of the device (N=2), and peri-prosthetic leakage (N=1). 86% of patients used a special lubricant to diminish stiffness of the valve. Provox ActiValve was preferred by 90% of the patients completing the trial specific questionnaire.

Conclusion: For patients requiring frequent device-related replacements, Provox ActiValve, also long-term, provides a true solution. Fistula related problems seem not increased. In these patients, who need frequent replacement, the ActiValve serves as a post-effective and thereby a valuable addition to prosthetic voice rehabilitation. Soolsma et al. Long-term results of Provox ActiValve, solving the problem of frequent Candida- and ‘underpressure’- related voice prosthesis replacements. Laryngoscope, 2007, in press.


Objectives: The primary purpose of this study was to assess for the first time the anatomical and morphologic characteristics of the pharyngoesophageal (PE) segment in tracheoesophageal (TE) speaking using an electroglossotrophography (Egg) based videostroboscopy tool. Study Design: Cross-sectional cohort study. Setting: Head and Neck Oncology Unit, tertiary referral centre. Patients: 52 patients following total laryngectomy with no recurrence and using prosthetic (Blom-Singer) speech. Intervention: EEG based rigid videostroboscopy and perceptual evaluation. Main Outcome Measures: Videostroboscopy protocol included 9 subjective/visual parameters that were used to evaluate the new tool and study correlation with the G of the GRBAS scale and the overall voice quality (OVQ) as well with the treatment variables. Results: Of the 52 patients in the study, videostroboscopy recordings were possible in only 46 patients (36 males and 10 females) with a mean age of 63.4 years (SD: +/- 10.5). All patients were using the Blom-Singer valve and the median time since TL was 2 years. Neoglottis was assessable in 26 patients and we were able
Lymphatic metastasis is the most important prognostic indicator in oral squamous cell carcinoma (OSCC). Current classification schemes for head and neck cancer are inadequate to predict prognosis. We hypothesize that there is a unique gene expression profile associated with OSCC-specific survival in patients with OSCC.

**Objectives:**

The primary objectives of this study were: 1) To determine whether a genetic expression profile associated with OSCC-specific survival can be used to predict survival in patients with OSCC. 2) To determine whether this gene expression profile is associated with patient demographic characteristics, tumor characteristics, and clinicopathologic variables. 3) To determine whether this gene expression profile is associated with survival outcomes in patients with OSCC.

**Methods:**

We performed hierarchical clustering on the expression of 131 candidate genes, identified by the Affymetrix U133 Plus 2.0 Plus array, in 119 OSCC, 35 normal oral mucosa, and 17 dysplasias. Linear regression was used to determine the differential gene expression between OSCC and normal oral mucosa and OSCC and dysplasias. Multivariate analysis using Cox-proportional hazards model was used to study the association of gene expression with survival outcomes. Hierarchical cluster analysis identified a group of 45 OSCC with a distinct expression signature, largely characterized by twelve probe sets that were down-regulated in the high-risk group. Principal component analysis revealed that there seems to be a continuum of gene expression such that survival outcomes appear to be related not only to the differential expression of the genes within this signature, but also to the degree to which these genes are up or down-regulated. Analysis based on stepwise Cox-proportional hazards regression revealed that the ability of our gene signature to discriminate OSCC patients based on survival outcomes is better than AJCC stage (C = 0.724) compared to 82.3 ± 0.06% for patients without the signature. Multivariate analysis using Cox-proportional hazards regression adjusting for age, gender and stage showed that patients with this genetic signature were at a significantly higher risk of OSCC-specific death compared to those without the signature (HR=5.4, 95% CI: 2.32, 12.73). Principal component analysis revealed that there seems to be a continuum of gene expression such that survival outcomes appear to be related not only to the differential expression of the genes within this signature, but also to the degree to which these genes are up or down-regulated. Analysis based on stepwise Cox-proportional hazards regression using the 131 probe sets revealed that a model containing LAMC2 (laminin, gamma 2) alone performed best at identifying patients with the worst OSCC-specific survival. Four additional models containing specific gene combinations also were strongly associated with OSCC-specific survival: 1) OSMR (oncostatin M receptor), PAI-1 (serpine peptidase inhibitor, clade E, member 1), and OASL (2'-5'-oligoadenylylsynthetase-like) combined; 2) SL1C16A1 (solute carrier family 16, member 1), KLF7 (Kruppel-like factor 7 ( ubiquitous)) alone; 3) CBP (CBP p300/CPB interacting protein 1, family member 1), member 1, and 202235_s_at combination. We identified a high-risk genetic expression signature that appears to be associated with OSCC-specific survival. The genetic expression data and TNM stage combined predicts OSCC-specific survival better than TNM stage alone.

**Results:**

- The image shows a schematic representation of lymphatic metastasis within tumor tissue, highlighting the lymphatic vessels and their role in the spread of cancer. The text is related to the biological mechanisms of SCCOT and associated lymphatic metastasis.

**Discussion:**

- The study suggests that there is a unique gene expression profile associated with OSCC-specific survival in patients with OSCC. This gene expression profile is associated with patient demographic characteristics, tumor characteristics, and clinicopathologic variables. Multivariate analysis using Cox-proportional hazards model was used to study the association of gene expression with survival outcomes. Hierarchical cluster analysis identified a group of 45 OSCC with a distinct expression signature, largely characterized by twelve probe sets that were down-regulated in the high-risk group. Principal component analysis revealed that there seems to be a continuum of gene expression such that survival outcomes appear to be related not only to the differential expression of the genes within this signature, but also to the degree to which these genes are up or down-regulated. Analysis based on stepwise Cox-proportional hazards regression revealed that the ability of our gene signature to discriminate OSCC patients based on survival outcomes is better than AJCC stage (C = 0.724) compared to 82.3 ± 0.06% for patients without the signature. Multivariate analysis using Cox-proportional hazards regression adjusting for age, gender and stage showed that patients with this genetic signature were at a significantly higher risk of OSCC-specific death compared to those without the signature (HR=5.4, 95% CI: 2.32, 12.73). Principal component analysis revealed that there seems to be a continuum of gene expression such that survival outcomes appear to be related not only to the differential expression of the genes within this signature, but also to the degree to which these genes are up or down-regulated. Analysis based on stepwise Cox-proportional hazards regression using the 131 probe sets revealed that a model containing LAMC2 (laminin, gamma 2) alone performed best at identifying patients with the worst OSCC-specific survival. Four additional models containing specific gene combinations also were strongly associated with OSCC-specific survival: 1) OSMR (oncostatin M receptor), PAI-1 (serpine peptidase inhibitor, clade E, member 1), and OASL (2'-5'-oligoadenylylsynthetase-like) combined; 2) SL1C16A1 (solute carrier family 16, member 1), KLF7 (Kruppel-like factor 7 ( ubiquitous)) alone; 3) CBP (CBP p300/CPB interacting protein 1, family member 1), member 1, and 202235_s_at combination. We identified a high-risk genetic expression signature that appears to be associated with OSCC-specific survival. The genetic expression data and TNM stage combined predicts OSCC-specific survival better than TNM stage alone.
Objective: The overall goal of this study is to develop independent and significant predictive measures of tumor behavior for head and neck squamous cell carcinoma (HNSCC). Methods: In our systems biology approach to study HNSCC, we extract tumors with TRizol® to isolate DNA, RNA and protein from the same piece of tissue for both independent and integrated analyses. We have developed and validated a method for detecting biologically significant differences in protein expression in two head and neck tumor cell lines (Sudha et al. Laboratory Investigation, 2007). The proteins from the cell lines, SCC25 and FADU, were isolated from the denatured protein solution remaining from the TRizol® procedure used for isolation of mRNA for microarray analysis. Peptides resulting from chemical and enzymatic digestion of the proteins were analyzed by 2D LC-MS. Of the ~40,000 signals, 90 peptide ions were found to discriminate the two cell lines with high stringency. This study demonstrates that this procedure is highly reliable for identifying peptides that distinguish biological variability among samples, and can therefore be used to identify potential prognostic biomarkers for predicting tumor behavior. In the present study 48 primary HNSCC specimens obtained from tongue, pharynx and larynx have been analyzed. Global proteomic analysis from these experiments is being used as a "training set" to discriminate/classify HNSCC with different clinical outcomes. When the entire data set was analyzed irrespective of tumor site, we identified 15 peptides that correlate with clinical outcome. Three peptides associated with node+ status, three were associated with local-regional recurrence, two were negatively associated with late-stage disease (II/IV), four were associated with time to disease progression or distant metastasis, and six were associated with disease-specific survival. Our initial attempts to analyze the three sites separately suggest that we can identify additional peptides that correlate with clinical outcome. Conclusion: The results strongly suggest that a small number of peptides can be used to develop a predictive model that can discriminate disease severity at initial diagnosis as well as clinical outcome prospectively. RNA expression profiling of primary HNSCC specimens have also been performed. We will integrate the proteomic data with the RNA expression data to identify the best potential prognostic biomarkers to develop clinical diagnostics. In the future, we will again refine and validate the predictive value of peptide discriminators by analyzing an additional 87 HNSCC samples as a "test set" with respect to tumor behavior and clinical outcome as well as obtain more precise estimates of effect.

Results:

TUMOR BEHAVIOR

A.Dolama, T. Belbin, N. Schleicht, M.Brandwein-Gensler, R.V. Smith, A. Bergman, Albert Einstein College of Medicine, Bronx, NY; Montefiore Medical Center, Bronx, NY

Objective: HNSCCs constitute an anatomically heterogeneous group of neoplasms, arising from diverse anatomic locations. To date, there is no biomarker that has been demonstrated to add value to the present TNM Staging classification system, the present gold standard. One of our ultimate goals is to identify a panel of prognostically significant biomarkers that can be evaluated on an initial diagnostic biopsy to assist in optimal treatment selection. The goal of this proposal is to characterize tumor behavior using systemic and computational biology approaches and correlate identified gene signatures with clinical data. Methods: Our initial data implied that the pattern of global gene expression in a HNSCC specimen contained information that could be used as a predictor of prognosis. The systemic approach to studying biological science is not new but it has gained tremendous momentum with the introduction of genome-wide expression profile analysis methods (Kitano, Nature 2002). We used a systemic approach to develop a new model for studying cancer biology, specifically in HNSCC. Our model characterized tumors as a complex network (or system) of cells and cellular processes that could be classified as aggressive or less aggressive. In this model, we define tumors as a system with cell communication ability to hide genetic expression information (i.e. metabolic robustness) (Bergman and Siegal, Nature 2003). This loss of robustness is characterized by high variability in expression of certain genes in the gene network of patient tumors. Results: In order to identify these variable genes, we first analyzed the expression profiles of 36 tumors versus universal tumor standard cDNA microarrays. We then classified these arrays into two groups based on the expression of cytoplasmic ezrin which correlates with decreased overall survival (Madan et al. Head and Neck, 2006). Our model isolates genes that deviate from equal variation between the two classes. Preliminary analysis of the 36 arrays identified a set of 117 highly variable genes with 109 genes highly variable in the high cytoplasmic ezrin tumors. We then performed cDNA microarrays comparing primary tumors to adjacent normal tissue in 35 HNSCC patients. An unsupervised cluster of the 117 variable genes clustered 34 of the 35 patients into 2 major groups (1-14 Patients) and 2 [20 Patients] and one outlier patient profile. Kaplan-Meier survival studies showed that patients in group 1 were more likely to have recurrence of tumors compared to group 2 (P-value = 0.0036). Furthermore, patients with higher recurrence probability exhibit down-regulation of immune system related genes. Conclusion: These results suggest that the 117 variable genes are able to predict probability of tumor recurrence. It also suggests a correlation between loss of immune response and increase in recurrence probability. In addition, we have identified a method of linking multiple biological backgrounds (different genotypes) to an observed pattern, namely HNSCC (phenotype).

S087: PROFILING OF MIRNA EXPRESSION PATTERNS IN HNSCC REVEALS TUMOR SPECIFIC SIGNATURES

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Objective: Head and neck squamous cell carcinomas (HNSCC) constitute an anatomically heterogeneous group of neoplasms, arising from diverse anatomic locations, including the oropharynx (OP), oral cavity (OC), and larynx/hyopharynx (HL). It is currently impossible to predict the behavior of tumors by histopathology due to a lack of appropriate biomarkers. miRNA expression patterns could provide more accurate correlations with clinical data than histologic or molecular markers for both diagnosis and treatment options. Our study is designed to test this hypothesis. Methods: We developed a miRNA microarray platform containing oligonucleotides complimentary to mature miRNAs. We compared global miRNA expression patterns of eight primary tumors and their corresponding adjacent normal mucosa. Differences detected by microarray analysis were further tested using real time PCR and confirmed our preliminary HNSCC miRNA signature. We then used Taqman quantitative real time PCR measurements of individual signature miRNAs on 187 different samples of primary tumors and adjacent normal mucosa where we have extensive clinical follow-up data. Tissue microarrays on many of these same samples were used to stain for PTEN protein whose expression is targeted by miR-21 that is commonly over-expressed in HNSCC tumors. Results: We used tumor to normal miRNA microarray comparisons to identify miRNAs that are aberrantly regulated in HNSCC. As is the case with other tumor models, HNSCC contain many miRNAs whose expression is altered. Many more miRNAs are expressed at lower levels in tumors than corresponding adjacent normal mucosa but miR-21 is frequently overexpressed. One confirmed target of miR-21 is the tumor suppressor PTEN that is known to be involved in HNSCC through LOH and mutation although this mechanism can not account for all tumors that lose PTEN. Tissue microarrays confirmed that every tumor with high miR-21 expression contain no or very low PTEN protein. We used Taqman quantitative RTPCR to measure miR-21, miR-205, let7d, miR-133a and miR-1 which are part of the HNSCC miRNA signature. Taqman assays on these 5 miRNAs and 187 RNA samples of primary tumors and adjacent normal mucosa where we have extensive clinical follow-up data were utilized to ask if predictions of outcome based on miRNA expression are feasible in HNSCC. Conclusions: HNSCC tumors have greatly altered miRNA expression profiles that can be measured using microarray and quantitative real time PCR assays. We predict that miR-21 along with LOH and mutation is involved in lowering PTEN activity in HNSCC. HNSCC signature miRNAs are being studied to ask if they can be used to improve diagnosis and clinical treatment decisions.
cated in tumorigenesis. The role of Ubc9 in Squamous Cell Carcinoma of the Head and Neck (SCCHN) has not been previously determined. In a previous study we have shown over-expression of Ubc9 in SCCHN compared to non-malignant adjacent mucosa and a correlation with clinical and pathological T stage, as well as a trend toward poor grade. The objective of this study was to determine the correlation of Ubc9 in SCCHN with tumor cell proliferation, using immunohistochemical (IHC) analysis.

**Methods:** A polyclonal Ubc9 targeting peptide was designed by mapping two previously harvested peptides from patients with a histologic diagnosis of SCCHN. Tissue specimens were snap-frozen in liquid nitrogen and stored at -80°C. Frozen tissues were stained with anti-Ubc9 antibodies using standard IHC techniques. Intensity of Ubc9 staining was determined on a 0 to 4+ scale in a blinded fashion, and was used to divide the patients into high and low Ubc9 expression groups. Tumors were staged according to the AJCC 2002 criteria. Proliferative index was determined by counting the positively stained nuclei for Ki-67 antibodies associated with hematoxylin visualized nuclei in five randomly chosen high-power fields. Statistically significant differences between Ki-67 expression and clinicopathological parameters were determined using a student t test. 

**Results:** IHC staining for Ubc9 was performed on a total of 45 primary tumors. Majority of the patients was 58 (range: 37-93), 73% were male and 96% were Caucasians. Thirty-eight of the 45 patients (84%) had advanced stage (Stage III & IV) disease with only 1% of samples representing stage I tumors. Sites of primary tumor specimens included larynx (n=16), oral cavity (n=16), and oropharynx (n=9). Forty (89%) patients were previously untreated for SCCHN and 5 (11%) had a history of prior treatment. Patients with a median age of 58 (range: 39-82) years had a median age of 58 (range: 39-82) years. The top target, EIF2c2, was then tested for over-expression by RT-PCR in HNSCC cell lines JHU-011, JHU-012, JHU-19, FADU and a normal oral keratinocyte cell line. EIF2c2 expression was determined by microRNA expression microarray (~12,000 genes) run on 6 normal tissues and 8 HNSCC tumor tissues. Significance Analysis of MicroArrays (SAM) was used to determine differentially expressed genes. The top target, EIF2c2, was then tested for over-expression by RT-PCR in HNSCC cell lines JHU-011, JHU-012, JHU-19, FADU and a normal oral keratinocyte cell line (OKF6). Expression of EIF2c2 was normalized to beta actin expression. Transfection of siRNA directed against EIF2c2 was performed. Cellular proliferation was assayed by MTT at 24, 48, and 72hrs. All experiments were run in triplicate. 

**Conclusions:** The published CGH array data by Sparano et al showed that the region (8q23.24-8q24.3) was amplified in 62% of their tumors. Within this region several genes were found, including EIF2c2 (eukaryotic translation initiation factor 2C, 2). The tumor tissues had an average microRNA expression level of 123 (SD=49) compared to the normal tissues 18.6 (SD=10) which had a p-value of 0.0005. EIF2c2 was also found to be expressed at a greater level in tumor tissue in 100% cases when using the greatest expression level in normal tissue as a threshold for tumor tissues. Normalized expression of EIF2c2 in cancer cell lines were JHU-011 (0.85 SD = 0.20), JHU-012 (0.69 SD = 0.08), JHU-019 (0.60 SD = 0.08), FADU (0.69 SD = 0.06). The minimally transformed oral keratinocyte cell line had an expression level of 0.56 (SD = 0.14). Since JHU-011 showed the highest expression level, it was chosen for siRNA knockdown of EIF2c2. MTT proliferation assay at 48hrs after transfection showed a 25% reduction in cellular proliferation and at 72hrs 37% reduction relative to transfected scrambled controls. 

**Conclusion:** MicroRNAs expression differences have been shown to play an important role in carcinogenesis. EIF2c2 is an argonaute protein which is involved in the RNA-induced silencing complex (RISC). RISC binds microRNAs which are then able to bind complementary strands and inhibit translation. This therefore has many implications for detection and therapy in HNSCC. Using two separate high throughput approaches were able to identify a candidate oncogene that is both amplified and over-expressed in cancer tissue that corresponds to the regulation of microRna. In addition, we were able to demonstrate not only was the cell line expressed in cancer cell lines, but also that knockdown of this gene could significantly inhibit cell growth.

**BASIC SCIENCE: EPIGENETIC, IMMUNE OR EXOGENOUS FACTORS**

**S090: EIF2C2, A RNA-INDUCED SILENCING COMPLEX (RISC) PROTEIN, IS OVER-EXPRESSED AND AMPLIFIED IN HNSCC S.S.Chang1, J.A.Califano1, 1Johns Hopkins Medical Institutions, Baltimore, MD**

**Objective:** The objective of this study is to identify the novel oncogenes/tumor suppressor genes that may contribute to carcinogenesis by integrating two high throughput approaches, high resolution CGH arrays and mRNA expression arrays of primary head and neck squamous cell tumor tissue. In addition, we validated our findings in cell lines. 

**Methods:** We combined published data from previously published regions of loss and/or gain with mRNA expression profiles to identify candidate oncogenes. Regions of loss/gain were identified from the profiling of 21 HNSCC using a high resolution (>1Mb) CGH arrays. Gene expression was determined by microRNA expression microarray (~12,000 genes) on 6 normal tissues and 8 HNSCC tumor tissues. Significance Analysis of MicroArrays (SAM) was used to determine differentially expressed genes. The top target, EIF2c2, was then tested for over-expression by RT-PCR in HNSCC cell lines JHU-011, JHU-012, JHU-19, FADU and a normal oral keratinocyte cell line (OKF6). Expression of EIF2c2 was normalized to beta actin expression. Transfection of siRNA directed against EIF2c2 was performed. Cellular proliferation was assayed by MTT at 24, 48, and 72hrs. All experiments were run in triplicate. 

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**Conclusion:** MicroRNAs expression differences have been shown to play an important role in carcinogenesis. EIF2c2 is an argonaute protein which is involved in the RNA-induced silencing complex (RISC). RISC binds microRNAs which are then able to bind complementary strands and inhibit translation. This therefore has many implications for detection and therapy in HNSCC. Using two separate high throughput approaches were able to identify a candidate oncogene that is both amplified and over-expressed in cancer tissue that corresponds to the regulation of microRna. In addition, we were able to demonstrate not only was the cell line expressed in cancer cell lines, but also that knockdown of this gene could significantly inhibit cell growth.
leading to metastasis. Our recent investigations indicate that inflammatory mediators are potent regulators of EMT in head and neck squamous cell carcinoma (HNSCC). **Objective:** To study the role of the inflammatory mediator IL-1b in E-cadherin regulation and EMT in HNSCC. **Methods:** Immunohistochemical analysis of HNSCC tumor tissue specimens, in vitro analysis of E-cadherin regulation in HNSCC cells, and in vivo analysis of tumors with EMT and metastasis in a murine model. **Results:** Head and neck tumors show significant downregulation of E-cadherin expression in response to IL-1b. This finding was confirmed by immunohistochemical staining of human HNSCC tissue sections. Second, treatment of HNSCC cells with IL-1b, which is known to be calcium dependent, Annexin II and Copine III were also identified as putative ligands. **Conclusions:** The further identification and characterization of these ligands will be tested. To confirm the function, HNSCC cells that express knock-down constructs of the putative ligands will be tested.

**S069: INTERLEUKIN 8 IS REGULATED BY TRANSCRIPTION FACTOR ATF2 IN HNSCC**

**Objective:** Determination of the regulatory mechanisms of IL-8 expression in HNSCC. **Methods:** IL-8 mRNA expression was determined using qRT-PCR in HNSCC cell lines and in normal oral epithelial cells. **Results:** The expression of IL-8 in HNSCC cell lines was significantly correlated with the expression of ATF2. **Conclusions:** ATF2 is a key transcription factor involved in the regulation of IL-8 expression in HNSCC. The identification of potential therapeutic targets for the treatment of HNSCC may be possible through the modulation of ATF2 activity.

**S070: PHOCYTES VIA L-SELECTIN**

**Objective:** To elucidate the nature of the interaction between L-selectin and leukocytes. **Methods:** Using an L-selectin affinity column, we isolated L-selectin-positive cells from peripheral blood mononuclear cells (PBMCs) from patients with HNSCC. **Results:** L-selectin-positive cells were isolated from patients with HNSCC. The adhesive interactions of these cells were characterized using flow cytometry and imaging studies. **Conclusions:** L-selectin-positive cells from patients with HNSCC show increased adhesive interactions, which may be due to the upregulation of L-selectin expression in these cells.

**S071: HEAD AND NECK SQUAMOUS CELL CARCINOMA MEDIATE LOW SHEAR-RESISTANT BINDING TO LYMPHOCYTES VIA L-SELECTIN**

**Objective:** To investigate the role of L-selectin in the interaction between HNSCC cells and lymphocytes. **Methods:** Using an L-selectin affinity column, we isolated L-selectin-positive cells from peripheral blood mononuclear cells (PBMCs) from patients with HNSCC. **Results:** L-selectin-positive cells from patients with HNSCC show increased adhesive interactions, which may be due to the upregulation of L-selectin expression in these cells. **Conclusions:** L-selectin-positive cells from patients with HNSCC show increased adhesive interactions, which may be due to the upregulation of L-selectin expression in these cells.

**S072: PROTEOMIC ANALYSIS OF LYMPHOCYTE-DEPENDENT ADHESION OF HNSCC CELLS**

**Objective:** To identify potential targets for the treatment of HNSCC. **Methods:** Using mass spectrometry, we identified protein modifications and changes in protein expression in HNSCC cells following lymphocyte interaction. **Results:** The expression of several proteins was significantly altered in HNSCC cells following lymphocyte interaction. **Conclusions:** These results suggest that specific protein modifications and changes in protein expression may be targets for the treatment of HNSCC.
NOMA CELLS (HNSCC)

S095: EPIGENETIC EFFECT OF GOSSYPOL IN THE IN VITRO SUPPRESSION OF HEAD AND NECK SQUAMOUS CELL CARCINOMA CELLS (HNSCC) C. Xi, Y. Wu, M.S. Koskela, P. Spring, R. Lee1, C. Chen. University of Arkansas for Med Sciences and VA MedCtr, Little Rock, AR; 2The Ohio State University, Columbus, OH; 3Univ Arkansas for Med Sciences, Little Rock, AR

Objectives: Gossypol, a male antifertility agent and a natural polyphenolic compound present in cottonseeds, has been shown to possess anti proliferative and pro-apoptotic effects both in vivo and in vitro in a variety of human tumors, such as HNSCC, prostate and breast cancer and hematologic malignancies. It has been shown that the tumor suppressive effects of gossypol is mediated through its potent inhibition of Bcl2 family of antiapoptotic proteins, protein kinase C, Cyclin D1, upregulation of transforming growth factor beta and induction of mitochondria-mediated apoptosis via activation of caspase family. We are presently reporting the novel epigenetic effect of gossypol in suppression of HNSCC.

Methods: Six HNSCC cell lines (UMSCC1, SQ-208, T-167, T409, TU167, and MDA198) and a normal oral keratinocyte cell line (HOK-168) were exposed to (-)-gossypol in the media at concentrations ranging from 0 to 64 µM for 6 days. Tumor necrosis was determined by determination of cell viability using trypan blue colorimetric assay.

Results: Separately, DNA samples were extracted from the above 7 cell lines before and after treatment with 0.5 µM gossypol. The DNA samples were then modified with sodium bisulfite and subjected to methylation-specific PCR (MSP) to characterize change in promoter methylation patterns for the following 7 genes that are frequently silenced via promoter hypermethylation in human malignancies: p16, MGMT, DAPK, E-cadherin, APC, TIG1 and RASSF1A. Results (-)-gossypol showed dose-dependent growth inhibition of 5 out of 6 (80%) HNSCC cell lines (UMSCC1, SQ-208, T-167, T409, and T167) at biologically achievable doses (less than 10 µM) with an IC50 ranging from 2.8 µM to 6.2 µM for these 5 cell lines. By contrast, normal keratinocytes, HOK-168, were less sensitive to (-)-gossypol with an IC50 of 26 µM. HNSCC cell line, MDA1986, was also relatively resistant to (-)-gossypol with an IC50 of 21 µM. By promoter methylation analyses of 7 different genes using MSP, the percentage of genes being methylated ranged from 71% (5/7) to 100% (7/7) in 6 HNSCC cell lines while that for normal keratinocytes was 25% (1/4). Following treatment of (-)-gossypol, the percentage of previously methylated genes that underwent promoter demethylation (complete or partial) varied from 60%/35% to 80%/45%. Among 6 HNSCC cell lines analyzed, UMSMC1 was most sensitive to (-)-gossypol with an IC50 of 2.8 µM and 80% of promoter demethylation while MDA1986 was most resistant with an IC50 of 21 µM and 65% of promoter demethylation induced by (-)-gossypol. Conclusions: Our results indicate that (-)-gossypol is an effective DNA demethylating agent for many tumor suppressor genes frequently methylated in HNSCC. In addition, the sensitivity of HNSCC to tumor suppressive effects of (-)-gossypol may be correlated in part with its DNA demethylation property.

S096: ANTIGEN SPECIFIC IMMUNE CLEARANCE OF HPV+ HNSCC REQUIRES CD4+ AND CD8+ CELLS R.L. Williams1, M.E. Anderson2, D.W. Lee2, J.H. Lee2. 1University of Iowa, Iowa City, IA; 2University of Iowa, Iowa City, IA

Objective: The incidence of Head and Neck Squamous Cell Carcinoma (HNSCC) has increased worldwide, in part due to Human Papilloma Virus (HPV). Several large studies examining survival after treatment have drawn a similar conclusion: HPV related HNSCC present at an advanced stage with more lymph node metastases (normal meaning worse survival), yet are 30-40% more curable than their corresponding HPV- counterparts. We hypothesize the increased survival can in part be explained by an anti tumor immune response to the HPV antigens present in the cells. To investigate whether HPV specific immune mechanisms can result in tumor clearance, we have created HPV+ and HPV- tonsil cancer cells in immune competent mice. In the following work we determine whether an immune specific response can clear HPV+ tumor cells and the cellular requirements to mediate this tumor clearance.

Methods: In past work we have developed methods to generate mouse models of epithelial cells. We have generated transformed mouse tonsil keratinocytes with similar oncogenic alterations. One cell line uses HPV E6 to transform the epithelial cells, hence HPV+. In a separate cell line we induce loss of a cellular target of E6 using a nonantigenic RNAi strategy. Both of these cell lines form SCCA upon implantation in wildtype mice. In the following studies we use classic immune strategies in syngeneic mice to understand the requirements for clearance of HPV+ cancers. Results: The HPV+ and HPV- cells have similar growth in vitro but different growth characteristic in vivo. The HPV+ cells universally form invasive tumors in the in wild-type mice resulting in death. In contrast, HPV+ cells demonstrated distinct growth phenotypes in wild type mice: 1) tumor progression to death or 2) clearance after 15 days. The HPV+ mice that spontaneously clear the tumors have a recall immune clearance upon reimplantation of HPV+ cells. Unlike wild type mice, immune deficient C57BL/6 and nude mice implanted with HPV+ tumor cells all have tumors that progress to death suggesting an immune response is required to clear the tumors. In vitro CTL analysis shows an antigen specific tumor response from the mice that clear tumors. To further understand the cells required for this immune mediated clearance we adoptively transferred WBCs from naive mice, mice that had spontaneously cleared their tumors to syngeneic Rag mice followed by HPV+ tumor challenge. The WBCs from cleared mice result in 100% clearance when transferred, while only 25% of WBCs transferred from naive mice cleared the tumor cells. Finally, antibody mediated immune depletion of CD4+ and CD8+ cells demonstrated that both of these cell types are required to clear the HPV+ tumor cells. Conclusion: Together, these data show that an in vivo antigen specific anti-tumor response is generated to HPV+ transformed cells and that this response requires CD4+ and CD8+ cells to mount this anti-tumor response. The findings from this preclinical model will have implications in not only understanding human disease but also be a valuable model for testing immunotherapeutic strategies for HPV+ HNSCC.

S097: TRIGGERING OF TLR4 OR TLR9 ON HUMAN HEAD AND NECK SQUAMOUS CELL CARCINOMAS (HNSCC) INDUCES DISTINCT BIOLOGICAL EFFECTS M. Szczepanski1, M. Szajnik1, M. Czytowska1, M. Harasymczuk2, W. Szyfter3, J. Zeromski3, E. Whiteside1. 1University of Pittsburgh Cancer Institute, Pittsburgh, PA; 2University of Medical Sciences, Poznan, Poland

Objective: Toll-like receptors (TLRs) which play a critical role in host defense against pathogens are key receptors of innate immunity. TLRs are expressed mainly on epithelial cells. We have previously shown that tumors can also be expressed on tumor cells including HNSCC. The aim of this study was to determine how functions of TLR4 and TLR9 contribute to HNSCC development. Methods: Tumor and control tissues were obtained from 15 patients with laryngeal and oral cavity tumors (disease stages III-IV). HNSCC cell lines (PCI-13, -13, -30) were established in our laboratory. RTPCR and immunohistochemistry assays were used to detect TLR4 and TLR9 expression at the mRNA and protein levels. Tumor cells were incubated with 10ug/mL LPS (TLR4 ligand), 0.4µM CpG ODN (TLR9 ligand) or with 2µM Paclitaxel (PLX). To assess tumor cell apoptosis Annexin V binding assay was used, and NF-kB translocation to nucleus was demonstrated by confocal microscopy following immunostaining of a p65 subunit. To show activation of the PI3K/Akt survival pathway, Western blots were performed. Cytokine levels in HNSCC supernatants were measured in Luminex-based multiplex cytokine assay. Results: TLR4 was expressed on 8/24 (33%) tumor specimens, showing membrane and/or cytoplasmic expression. TLR9 was expressed in the cytoplasm of 20/24 (83%) tumor specimens. TLR4 and TLR9 were also expressed at mRNA and protein levels on all tested tumor cell lines. LPS binding to TLR4 induced resistance to PLX-mediated apoptosis (p<0.05) via activation of the PI3K/Akt pathway. TLR4 triggering also induced nuclear translocation of NF-kB in HNSCC cells and increased production (p<0.05) of IL-6, IL-8 and VEGF relative to controls. In contrast, triggering of TLR9 by CpG induced exactly opposite response. Conclusion: Our results indicate that TLR4 stimulation on tumor cells supports tumor progression, while activation of TLR9 inhibits tumor cell growth and sensitizes tumor cells to drug-mediated apoptosis. Strong expression of TLR9 in HNSCC suggests that this receptor could be a potential target for cancer therapy.

S098: CONSISTENT ABERRANT DNA METHYLATION EVENTS IN LARYNGEAL PAPILLOMAS IMPLICATE AN EPIGENETIC CONTINUUM TO MALIGNANCY J.K. Stephen1, K. Chen1, L. Vaught1, V. Shah1, V.G. Schweitzer1, G. Gardner1, M.S. Benninger1, M.J. Worsham1. 1Henry Ford Hospital, Detroit, MI

Objective: Laryngeal papillomas usually run a benign but recurrent course. Epigenetic events of DNA hypermethylation have been shown to underlie the pathogenesis of recurrent respiratory papillomas (R RP), some of
which are initiating clonal alterations in the recurrence continuum in some RRP cases. In the spontaneous transformation of recurrent RRP to squamous cell carcinoma (SCC), a progression continuum to malignancy may not be histologically and clinically apparent, making these lesions difficult to diagnose early in the course of the transformation of the disease. This study examined whether epigenetic events of aberrant promoter methylation contribute to the transformation to malignancy continuum in RRP. **Methods:** A retrospective study of 26 cases of OSCC containing laryngeal papilloma biopsy between the years 1994 through 2004, with follow-up for subsequent transformation to severe dysplasia, carcinoma in situ, or squamous cell carcinoma through May 2007 was examined. Archival tissue DNA was interrogated for aberrant methylation status of 22 methylation-prone tumor suppressor genes using the methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) assay. Methylation specific PCR (MS-PCR) was performed to confirm aberrant methylation detected by MS-MLPA. **Results:** Of the 26 cases, 15 were RRP. Promoter hypermethylation was recorded in 24 of 26 cases. Twenty of the 22 tumor suppressor genes in the multi-gene panel had altered DNA methylation in at least 1 or more laryngeal papilloma tissues. Ablation of DNA methylation of CDKN2B and TIMPS genes was most frequent. MS-PCR for CDKN2B, performed for RRP cases 4, 7, 11, and 12, confirmed aberrant methylation by MS-MLPA. In two RRP cases that progressed to malignancy, aberrant DNA methylation of BRCA2, and CDKN2A and CDKN2B in Case 1 and Case 5, respectively, was observed in the subsequent squamous cell carcinoma. **Conclusion:** Consistent aberrant methylation of multiple tumor suppressor genes contributes to the pathogenesis of laryngeal papillomas. Ablation of DNA methylation is a defining benign RRP and in the subsequent malignant lesions implicates an epigenetic monoclonal progression continuum in the transformation to SCC. Because promoter hypermethylation is potentially reversible, the molecules that regulate methylation status of DNA are considered promising targets for new cancer therapies. These DNA methylation signatures could serve as biomarkers of risk assessment and early detection, and as molecular targets for treatment and chemopreventive interventions.
Patients with cancer of the upper respiratory tract who receive HPV DNA was detected in 7/7 OSCC and in 2/10
An approved IRB CI-1040 inhibits PTC cell growth in
Hematoxylin and
Tumor-derived microvesicles (MV) expressing a membrane form
Patients with advanced head and neck squamous cell carcino-
proffered papers
S.Rubinchik T.McRackan L.Halstead M.B. Gillespie N.A. Surtovskii Medical University of South Carolina, Charleston, SC
Human papillomaviruses (HPV) are established as causative agents of cervical carcinoma and are increasingly accepted as etiological factors in oropharyngeal squamous cell carcinoma (OSCC). We discovered that HPV16 oncoproteins E6 and E7 transactivate an endogenous superantigen in human tonsil and adenoid epithelial cells. The superantigen is encoded by human endogenous retrovirus HERV-K18, a defective primate Rous sarcoma virus. Methods: 17 head and neck tumors were identified by the operating surgeon as high or low risk for HPV infection. Frozen tissue from 7 OSCC (high risk), 10 tumors from other sites (low risk), and 10 benign uvulae specimens were tested for HPV infection by DNA PCR, using degenerate primers that amplify known HPV types. HPV typing was performed by restriction enzyme cleavage analysis of the amplification products. Total RNA was simultaneously extracted from all samples and expression levels of HPV E6 and E7 oncogenes, and the HERV-K18 superantigen were quantified by real-time RT-PCR. For transactivation studies, adenoviral vectors expressing HPV16 E6, E7, E6/E7, or EGFP genes were used to transduce primary keratinocytes cultured from surgical tonsil and adenoid specimens. 24 hr post-infection, total RNA was analyzed for superantigen expression by quantitative RTPCR. Results: HPV DNA was detected in 7/7 OSCC and in 2/10 other tumors, but not in benign uvulae (0/10). High risk type 16 was identified in all positive cases. HPV E6/E7 expression was detected in 5/7 OSCC, and in 2/10 other tumors. HERV-K18 superantigen expression levels correlated with HPV E6/E7 expression. Statistically higher levels of superantigen expression were detected in tumors expressing HPV E6/E7 compared with negative tumors (p = 0.042), or benign uvulae (p = 0.001). No difference was seen between E6/E7- tumors and benign uvulae (p = 0.22). Quantitative RTPCR demonstrated that superantigen expression was upregulated in primary oropharyngeal (> 10 fold) and nasopharyngeal (> 10 fold) keratinocytes, following adenoviral transduction of HPV16 E6, E7, or both oncogenes. Conclusions: A statistically significant correlation was found between expression of HPV E6/E7 oncogenes and HERV-K18 superantigen expression, both in OSCC and in cultured primary oropharyngeal and nasopharyngeal keratinocytes. We postulate that the HERV-K18 superantigen stimulates T cells in the tumor microenvironment of HPV+ OSCC, influencing tumor immune surveillance and clinical outcome. While some studies suggest that chronic inflammation promotes carcinogenesis, the presence of HPV in OSCC correlates with a more favorable clinical outcome. Thus, it is tempting to speculate that localized inflammation induced by the HERV-K18 superantigen enhances immunosurveillance in HPV+ tumors, thereby predisposing them towards a favorable outcome.

S103: ENGINEERING AN ARTIFICIAL SALIVARY GLAND S.Prado 1, M.C. Farach-Carron 2, X.Jiaa 3, C. Zhang 3, R.L. Whitt 4

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Objective: Patients with cancer of the upper respiratory tract who receive radiotherapy suffer from xerostomia. Direct radiation damage of the acinar cells that secrete fluid and protein results in salivary gland dysfunction. Medical management of xerostomia has not been satisfactory. Salivary gland tissue engineering has produced ductal, but rarely pure acinar cells in culture. Acinar cell forms clusters and when dissociated are frequently damaged. The goal is to culture pure acinar cells capable of polarizing and to ultimately engineer a functional artificial salivary gland capable of unidirectional fluid movement, and membrane barrier function that can be implanted into patients. A prototype artificial gland is generated by coating the inner surface of an artificial blind end hyaluronic acid-based hydrogel tube with native extracellular matrix (ECM) to support a functional monolayer of secretory salivary gland epithelial cells. Hyaluronic acid plays pivotal roles in cell differentiation and cell mobility. Methods: An approved IRB protocol for salivary gland tissue procurement was obtained from patients undergoing routine salivary gland surgery. Histology and immunohistochemistry with specific markers were used to establish the phenotype of normal salivary gland cells. This source of cells was cultured to develop a 3-D cellular system for culturing ductal and pure acinar cells. The ability of cultured cells to mimic native cells in salivary gland was assessed. Parallel to the rat was used as an animal model for cell culture. To engineer the artificial salivary gland, a pliable hydrogel tube was constructed of crosslinkable hyaluronic acid. Natural ECM micromers of basement membrane components present in salivary gland epithelial cells. Hyaluronic acid plays pivotal roles in cell differentiation and cell mobility. Results: Hematoxylin and Eosin staining confirmed normal glandular tissue structures including intercalated ducts, striated ducts and acini. 3B1-amylase and Periodic Acid Schiff stain, used for structures with a high proportion of carbohydrate macromolecules, preferentially stained acinar cells in the tissue. Intercalated and striated duct structures were identified using cytokeratins 19 and 7 staining. Myoepithelial cells positive for cytokeratin 14 were found wrapped around the serous and mucous acini. Analysis of the ECM of the salivary gland revealed large amounts of perlecan/HSPG2, a component of ECM which can be used for coating the hydrogels. Tight junction components including ZO-1 and E-cadherin were present between both ductal and acinar cells. Cultured cell sub-populations including pure acinar cells were completely successful in expressing all of these tissue markers. Cultured cells were noted to spontaneously form tube-like structures under certain conditions. Functional integrity of cultured salivary gland cells was measured by increases in transepithelial electrical resistance and compared to an established kidney cell line that correlated with expression of tight junction proteins. Conclusions: Pure acinar cells capable of spontaneous tube formation were successfully cultured. A system for isolation and maintenance of salivary gland primary cultures suitable for tissue engineering is reported. Further studies are designed to test the performance of these cells on different ECM including those derived from perlecan and laminin and analyze the expression of aquaporins and sodium-potassium ATPase in primary cells.

S104: IRX, A MULTI-TARGETED BIOLOGIC, PROTECTS HUMAN T CELLS FROM TUMOR-INDUCED CELL DEATH M. Czaytowska 1, M. Szczepanski 1, M. Szaunyik 1, T.L. Whiteside 1, K. Quadrini 2, K. Szajnik 1, T.L. Whiteside 1, 1University of Pittsburgh Cancer Institute, Pittsburgh, PA; 2IRX Therapeutics, Inc., Farmington, NY

Objective: Patients with advanced head and neck squamous cell carcinoma (HNSCC) demonstrate local and systemic immune suppression, which is thought to be due to tumor-induced apoptosis. IRX-2 is a dual-targeted biologic with multiple active components including: interleukin-1382 (IL-1382), IL-2, IL-6, tumor necrosis factor-α (TNF-α), granulocyte macrophage colony stimulating factor (GM-CSF), and interferon-β (IFN-β). IL-1382, IL-2, and IFN-β are interferon-stimulating cytokines that induce tumor immunity by augmenting the immune response to tumors. Methods: Tumor-derived microvesicles (MV) expressing a membrane form of Fas, were purified from supernatants of the PCI-13 cell line and co-incu-
S105: INVOLVEMENT OF RAS SUPERFAMILY (RHOC) IN HEAD AND NECK METASTASIS

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Purpose: Despite the tremendous advancement in surgery, chemo and radiation therapy, the survival rates for head and neck squamous cell carcinoma (HNSCC) have not changed significantly in past several decades due to local recurrence and distant metastasis. Furthermore, it has been shown that the Ras superfamily is critical in transforming localized cancerous cells into metastatic phenotypes. Among this protein superfamily, RhoC plays a central role in metastasis, even in small cancers. In this study, we will investigate the correlation between RhoC expression and the metastatic behavior of HNSCC.

Methods: The inhibition of RhoC activity was achieved using small interfering RNA (siRNA) and the recently developed lentiviral transfection and interfering RNA (siRNA) and the recently developed lentiviral transfection and gene delivery technology. Briefly, the UM-SCC11A and 36 squamous cell carcinoma cell lines were transduced with highly modified lentiviral vectors that carry small sense and anti-sense sequences against the RhoC gene. In the transfected cells, these sequences are transcribed into small hairpin degradations that targeted RhoC mRNA. To test the infection efficiency, the cells, signifying a high efficiency of transduction. qRT-PCR of Lentivirus infected cell lines showed 70-80% reductions in gene expression in RhoC mRNA-degrading machinery that targeted RhoC mRNA. To test the infection efficiency, the cells were analyzed for activation, degranulation and cytokine secretion.

Results: Significant decreases in lung metastases in SCID mice implantation for in vivo studies. qRT-PCR and qRT-PCR, cell invasive and motility assays were performed according to the standard procedure. SCID mice were used for tail vein and flank cell implantation for in vivo studies. Positive clones were selected using Puromycin antibiotic. Fluorescence microscopy of the stable clones showed a strong green fluorescence in the majority of the cells, signifying a high efficiency of transduction. qRT-PCR of Lentivirus infected cell lines showed 70-80% reductions in gene expression in RhoC knockdown. Furthermore, Western blots analysis illustrated 50-70% decrease in protein in RhoC knockdown cell lines as compared to its parental counterpart. Cell motility and invasive behavior were also markedly diminished in RhoC-depleted cell lines as compared to parental lines. Hematoxylin and eosin staining of lung tissue obtained from in-vivo experiments showed dramatic decreases in lung metastases in SCID mice implanted with parental and or cell lines transduced with siRNA scrambled control as compared to RhoC knockdown clones. CD 31 staining of tumor revealed qualitative differences in the primary tumor microvessel density. The sizes and number of new vessels in RhoC knockdown tumors were significantly decreased as compared to its parental counterpart and siRNA scrambled control.

Conclusion: This study is the first of its kind to establish the involvement of RhoC in head and neck cancer metastasis. These findings suggest that RhoC may be a novel target for biologic therapeutic targeting in the future.
activity. These immune effects appear to be independent of EGFR expression on tumor cells, consistent with observations in cetuximab treated patients. ADCC activity by PBMC from advanced disease stage and poor responder genotypes can be improved with cytokine treatment. Serum cytokine levels or Fcγ receptors from patients’ peripheral blood may provide clinically useful immune biomarkers in cetuximab treated patients.

S108: LEVELS OF CD44, A HEAD AND NECK CANCER STEM CELL MARKER CORRELATE WITH TUMOR AGRESIVENESS

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Objectives: A subpopulation of CD44+ cells with cancer stem cell (CSC) properties was previously identified by flow-cytometry in head & neck squamous cell carcinoma (HNSCC). The current study correlates known prognostic clinical-histological factors with stem cell activity, hypothesizing that increased CSCs correlate with poor prognosis. Methods: The study included 31 patients with HNSCC, 87% with Stage IV, with mean follow-up 12.9 months. Success of passing tumors to immunocompromised mice and percent of CD44+ cells analyzed by flow-cytometry were correlated to clinical and pathological data including: TNM, type of treatment, outcome, tobacco use, histologic grade, perineural invasion (PNI), extra-capsular extension, and angiolymphatic invasion. We will present this data with an update of an additional 15 cases from Stanford and 27 cases from U. Michigan.

Results: CD44+ cells were assayed in 22/31 tumors. Mean level of CD44+ was 25% (0.4-81%). Its levels were higher in advanced T stage (p=0.05). Mean CD44+ was 36% in patients with recurrence vs 15% for non-recurrence (p=0.04). It was borderline correlated to grade. Successful xenograft implantation was observed in 16/30 (53%) tumors. It was correlated to CD44+ level (p=0.009), histological grade (p=0.015), and recurrence (p=0.003): of 16 successful explants 12 recurrent vs 3 recurrences among 14 unsuccessful xenografts (p=0.003). In a Cox model CD44% was found to be most significant indicator of survival (p=0.045).

Conclusions: Successful xenograft and high percentage of CD44+ correlate with poor prognostic factors as advanced T stage and recurrence. These findings lend initial, albeit preliminary, clinical support to the concept that SCC stem cells are important in cancer biology, correlating with aggressive characteristics.

CLINICAL: PARATHYROID/THYROID

S109: ACCURACY OF SPECT/CT HYBRID IMAGES IN PREDICTING THE INTRAOPERATIVE LOCATION OF PARATHYROID ADE- NOMAS L.D. Harris1, J. Yoo1, A. Driedger1, K. Fung1, J. Franklin1, D. Gray1, R. Holliday1, 1University of Western Ontario, London, ON, Canada

Background: This study evaluated the accuracy of SPECT/CT imaging for the preoperative localization of parathyroid adenomas. Methods: This study included both a quantitative and qualitative accuracy measure. The quantitative measure was the distance between the location of the adenoma on the SPECT/CT scan and the location of the adenoma intraoperatively. Qualitatively, surgeons were asked whether or not the adenoma was in the exact location predicted by the SPECT/CT scan. The time from initial incision to identification of the parathyroid was recorded. Patients referred to London Health Sciences Centre for a suspected parathyroid adenoma were eligible for this study.

Results: Twenty-three patients participated in this study. Eighteen (78.3%) had a single adenoma, two (8.7%) had double adenomas, and three (13.0%) had multiglandular hyperplasia. SPECT/CT correctly detected and localized 18 of 18 (100%) cases of single parathyroid adenomas. The mean distance between the location of the adenoma on the SPECT/CT scan and the location of the adenoma intraoperatively was 16.3 mm (95% CI 9.4-23.2 mm). Conclusions: SPECT/CT predicted the intraoperative location of a single parathyroid adenoma within 19.0 mm with 95% confidence. The correct detection and localization of multiglandular disease remains difficult.

S110: THE USEFULNESS OF METHYLENE BLUE INFUSION IN PARATHYROIDECTOMY FOR SECONDARY HYPERPARATHY-ROIDISM J. Lah1, D. Kim1, Y. Jung1, K. Kim1, M. Sung1, 1Department of Otorhinolaryngology, Seoul National University College of Medicine, Seoul, Republic of Korea

Objective: In the patients with secondary parathyroidism, localization of all parathyroid glands is often difficult to surgeons. The aim of this study was to evaluate the usefulness of intraoperative methylene blue infusion for localization of all parathyroid glands in secondary hyperparathyroidism.

Methods: This study was designed prospectively. From September 2007 through August 2007, eight patients with secondary hyperparathyroidism underwent parathyroidectomy for the treatment of secondary hyperparathyroidism using the surgery, intraoperative methylene blue infusion was used for localization of parathyroid glands. Results: In all cases, all parathyroid glands were well stained with methylene blue. The procedures were done easily without any complication. After operation, all patients were well controlled in symptoms and calcium levels in blood serum.

Conclusion: The intraoperative methylene blue infusion is an effective method for localization of all parathyroid glands in secondary hyperparathyroidism.

S111: MINIMALLY INVASIVE PARATHYROIDECTOY

Until 1980, parathyroid surgeons considered exploration of all parathyroid glands to be mandatory, but recent innovations have expanded the surgical approaches to primary hyperparathyroidism. The availability of new imaging techniques, i.e., ultrasonography (US) and sestamibi scintigraphy (MIBI), and the intraoperative quick parathyroid hormone (QPTH) assay led to the development of minimally invasive parathyroidectomy. US has been successfully used to establish the excellent accuracy for the localization of parathyroid glands. US images have recently been converted from 2D to 3D imaging organs. We used real-time 3D US for small parts and evaluated its efficacy and clinical usefulness for parathyroid surgery. The transducer is built into the 4D probe and swings through maximum angle of 90 degrees. The horizontal (coronal) section was a new image that had never been possible to observe by US before. Since it was very close to the intraoperative view, it provided an efficient method of preoperative localization and served as a diagnostic modality for surgeons. We were also able to acquire volume data with the 4D transducer. The color mode was allowed observation the vascular structures. MIBI and double-phase MIBI were subsequently introduced with the aim of improving the accuracy of localization, reducing surgical time, improving cosmesis, and increasing cost-effectiveness. Although radioguided parathyroidectomy is a viable alternative to standard surgery for properly selected hyperparathyroid patients with no history of exploratory procedures in the neck region, it is also useful in patients with hyperparathyroidism who have undergone previous exploratory neck procedures. Parallel to this development, several minimally invasive parathyroidectomy procedures have come into widespread use for the treatment of hyperparathyroidism. The minimally invasive procedures range from the pure endoscopic approach (completely closed technique) characterized by minimal incisions to more exposed techniques with limited gasless approaches and minimally invasive mini-incision parathyroidectomies guided either by intraoperative radioisotopes or relying on preoperative localization studies. The minimally invasive procedures can be classified as minimal-access surgery and provide both a more acceptable cosmetic scar and a less painful postoperative course than conventional procedures. Its disadvantages include longer operating time, a supposedly higher cost, and the possible risk of missing multiparathyroid disease. Minimally invasive parathyroidectomy techniques will probably play an increasingly large role in the management of hyperparathyroidism. Superior sternum lifting method was used to remove ectopic large parathyroid gland deep in the anterior mediastinum that would have other-wise required median sternotomy or thoracoscopic procedure, where the exact anatomic location of the parathyroid gland was established preoperatively. Electrical identification & monitoring of the recurrent laryngeal nerve (RLN) has been proposed as an adjunct to standard visual identification of the nerve during thyroid & parathyroid surgery. We report the usefulness of laryngeal electromyographic (EMG) monitoring (Nerve Integrity Monitoring, NIM, system). The new minimally invasive technique described above is expected to lead to improved patient comfort, shorter hospital stays, and favorable cosmetic results in a select group of patients, and this operative procedure may be performed on an outpatient basis.

S112: PARATRACHEAL NECK DISSECTION: INDICATIONS, TECH- NIQUE AND RESULTS.

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Treatment of the paratracheal region in patients with thyroid cancer remains an issue of controversy among head and neck surgeons. The purpose of the current study was to review the indications, surgical technique and results following paratracheal neck dissections for thyroid cancer. Methods:
Eighty-nine patients undergoing unilateral or bilateral paratracheal neck dissection (PTND) were prospectively evaluated. Eighty-four patients had papillary carcinoma with either unilateral or unilateral regional metastases/recurrences. Five patients had medullary thyroid carcinoma. Calcium levels were monitored in all patients for a minimal period of 72h.

**Results:** All patients recovered from the surgical procedure with no major morbidity. Four patients suffered from inadvertent recurrent laryngeal nerve injury that completely recovered in all of them. In four patients (two of whom had pre-operative RIN paralysis) the recurrent laryngeal nerve was resected along with an aggressive tumor invading it. Transient hypocalcemia was noticed in 16 patients (18%) but only one (1%) remained hypocalcemic one year following the surgical intervention. The incidence of hypocalcemia was significantly higher in patients that had a bilateral PTND compared with unilateral PTND (44% vs 12%). Calcium supplementation was required in 31 patients (35%); the incidence of PTND is a safe procedure. Injury to the recurrent laryngeal nerve is uncommon. Hypocalcemia is more common when bilateral paratracheal neck dissection is performed and is almost always transient.

**S113: BILATERAL SUPERFICIAL CERVICAL PLEXUS ANESTHESIA FOR THYROID SURGERY: PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY**

**Introduction:** Thyroid surgery is a well known surgical procedure and it can be painful for patients specially the first 48 hours. The average VAS score recorded was 6, and as many as 90% of patients will need opioid for adequate analgesia. Regional anesthesias for cervical surgery as cervical pereidural anesthesia or profound cervical plexus blockade are invasive procedures with associated complications. Using local anesthetics placed in the paravertebral space or regional nerve blocks may be useful for these patients, specially used before the surgical stress (preventive analgesia). **Objective:** evaluate the benefit and the quality of bilateral superficial cervical plexus blockade in the postoperative of thyroid surgery. **Method:** patients selected for thyroid surgery under general anesthesia, without contraindications for any drug, were studied. Conventional balanced anesthesia with fentanyl, propofol, vecuronium and isoflurane were used. We random created two groups: placebo (A) and bupivacaine 0.25% (B). After induction of general anesthesia the surgeon proceeds with conventional superficial cervical plexus infiltration with 10 cc each side of the neck. All the attending medical team were blind to the content of the syringe (bupivacaine or physiologic solution). Post operative pain, PCA morphine requirements, adverse events and patient satisfaction were recorded. **Results:** 35 patients were studied: 15 in group A and 20 in group B. Average age of 55.3 ± 14.8 years old. The average morphine use was 10.4 mg in group A and 5.8 mg in group B. This was statistical significant (p< 0.05). In the bupivacaine group (B) 25% of patients did not use morphine at all, whereas in the placebo group all patients used morphine. The presence of nausea and vomiting was also statistically significant: 93% in group A and 21% in group B. The use of analgesics medication for nausea and vomiting was an average of 4.6 mg of ondansetron in group A and 2.1 mg in group B (<p=0.05). The patients satisfaction score was not different between groups. No complications of the procedure were recorded. **Conclusion:** Bilateral superficial cervical plexus blockade with bupivacaine 0.25% is a very good adjuvant for thyroid surgery. Their use allows the diminution of pain, nausea and vomit in the post operative.

**S114: OUTPATIENT THYROIDECTOMY: EXPERIENCE IN OVER 200 PATIENTS**

**Objectives:** Thyroidectomy is historically performed on an inpatient basis out of fear of hemorrhage and transient but life-threatening hypocalcemia. An earlier favorable experience with outpatient surgery for a limited number of patients prompted an expanded evaluation of this practice. **Design:** Prospective, non-randomized analysis of a consecutive series of surgical patients undergoing thyroidectomy in an academic otolaryngology department. **Methods:** After institutional review board approval was obtained, patients undergoing thyroid surgery between 2/26/03 and 11/14/07 were identified and segregated based on admission status. Demographic data including age and gender were extracted and clinical variables including type of surgery, indications, length of hospital stay and complications were obtained and analyzed. The primary outcome measures were duration of hospital stay, incidence of complications, and rate of readmission. **Results:** 418 patients underwent thyroid surgery. 208 were accomplished on an outpatient basis, 130 patients were observed under a 23-hour status, and 80 were admitted for a mean of 2.9 days (the latter 2 cohorts were grouped together and designated as inpatients). There were 14 complications in the outpatient group (6.7%) and 37 (17.6%) in the inpatient group (p = 1.0). Four individuals in the outpatient group (1.9%) required readmission compared with 5.7% (12/210) of those in the inpatient group, most commonly for transient hypocalcemia. **Conclusions:** The initial favorable experience with outpatient thyroid surgery has been validated in this expanded patient population. Modern surgical techniques, avoidance of drains, and prophylactic calcium supplementation have combined to make outpatient thyroidectomy safe in carefully selected patients.

**S115: COMPARISON OF TRENDS IN INCIDENCE AND MORTALITY FROM THYROID CANCER IN THE UK AND THE USA**

**Background:** The incidence of thyroid cancer is known to have increased in the USA in recent years. Mortality on the other hand appears to have remained stable. It is not known whether this is peculiar to the US or part of a general trend worldwide. Understanding this may help identify possible reasons for these trends. **Objectives:** 1. To examine the trends in incidence and mortality from thyroid cancer over a 25 year period in UK, and 2. To compare those trends with that of the USA. **Methods:** The West Midlands Cancer Intelligence Unit (WMCIU) gathers statutory data on newly-diagnosed cancer cases diagnosed within the West Midlands region, covering a population of 5 million people. The borders of the region have remained unchanged over the past 25 years, thus providing a stable population base to study. Using data from the WMCIU Cancer Registry database, we have examined trends in incidence and mortality rates from thyroid cancer over a 25 year period, and compared it to data from Surveillance Epidemiology and End Results (SEER) in the USA (1). Data was analysed using t test. Indicators of data quality and accuracy were also assessed to understand the effect of data gathering on the accuracy of the data utilised. **Results:** From 1981 to 2004, the incidence rate of thyroid cancer in the West Midlands has increased significantly from 1.83 to 2.96 per 100,000 population (62% increase) (<p=0.05), compared to a significant 122% increase in USA [4.4 to 9.8 per 100,000] over the same duration (<p=0.05). Over the same time period, the mortality rate in West Midlands has improved by 56% from 0.94 to 0.41 per 100,000 (<p=0.05). In the USA, mortality rate has remained stable at 0.4 - 0.5%. Mortality / incidence ratio decreased over the period in the West Midlands from 0.52 to 0.16. In the USA, it has also had a similar improvement from 0.1 to 0.05 (43% improvement) over the same period. **Conclusions:** The incidence of thyroid cancer in both the UK and USA has increased considerably over the last two decades. Interestingly, thyroid cancer is twice as prevalent in the US as in the UK, and is increasing at twice the rate of the UK. Mortality rates in recent years in both regions have improved to US levels, but the mortality to incidence ratio remains better in the USA. We discuss possible reasons for the increase in incidence and the improvement in mortality, including causes of mortality, stage of disease and treatment regimens. **Reference:** 1. Surveillance, Epidemiology, and End Results (SEER) Program [www.seer.cancer.gov] SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use, Nov 2006 Sub (1973-2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.

**S116: EFFICACY OF RECURRENT LARYNGEAL NERVE MONITORING IN AN OTOLARYNGOLOGY ACADEMIC TRAINING PROGRAM**

**Objective:** Recurrent laryngeal nerve (RLN) monitoring is a useful tool to provide feedback during dissection that may aid in nerve identification and subsequently reduce nerve injury. The objective of this study was to examine the efficacy of a RLN monitoring system in anatomical nerve identification and evaluate RLN injury from surgery in a training program that employs highly active resident participation. **Methods:** During a retrospective three year period, attending surgeons with senior residents performed thyroid and parathyroid surgery at a tertiary care academic center on 177 patients with 247 nerves at risk. A Medtronic Xomed® NIM™ EMG reinforces endotracheal tube was placed to monitor intrinsic laryngeal muscle activity and RLN stimulation. Audiologists trained in intraoperative electrophysiological techniques performed the monitoring. The primary outcomes measured were anatomical identification of the RLN, permanent nerve paralysis, and nerve transaction.
Results: 247 nerves at risk (100%) from thyroid or parathyroid surgery were identified during surgery. There was one RLN that was identified as transected at the end of the case. This patient had sufficient voice recovery that did not require further intervention for voice performance. There were no other permanent RLN paralysis identified. Conclusions: EMG RLN monitoring utilizing endolaryngeal electrodes provides an effective resident teaching tool to aid in precise anatomical identification of the RLN. However because the baseline risk of severe RLN injury is low, nerve identification with EMG monitoring cannot be definitively linked to reduced rates of injury. RLN monitoring should not replace sound surgical technique and knowledge of anatomy but augment these skills to provide additional levels for patient safety and optimal outcomes.

S117: THYROIDECTOMY SCAR LENGTH AND POST-OPERATIVE SCAR SATISFACTION: A RANDOMIZED CLINICAL TRIAL

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Objective: The primary objective was to determine if scar length in thyroidectomy affects patient’s satisfaction with their scar. The secondary objective was to determine if there is any increase in post-operative complications following thyroidectomy through a smaller incision. Methods: Consent was obtained from all participants to randomize to have their thyroidectomy by the standard 10 cm incision, or a shorter 5 cm incision. Postoperatively the patients were evaluated at 2 weeks, 1 month, and 3 months. Their thyroidectomy scar was evaluated subjectively by the patient using the “patient and observer scar assessment scale” and objectively by using the “Vancouver scar scale.” Results: When comparing the 5 cm and 10 cm incision groups, there is no clinically significant difference in subjective patient satisfaction with their scar at any time point, using the patient and observer scar assessment scale. Objective assessment using the Vancouver scar scale also failed to find a clinically significant difference. In addition there is no difference in the post operative complication rate between the two groups. Conclusion: In thyroid surgery the length of the incision appears to have little effect on cosmetic outcomes when comparing a standard 10 cm incision with a minimally invasive 5 cm incision.

RISK FACTORS/PREVENTION/SCREENING

S118: EARLY RESULTS OF A LONG-TERM SCREENING PROGRAM FOR NASOPHARYNGEAL CARCINOMA: EVIDENCE FOR SCREENING HIGH RISK COHORT

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Objectives: The siblings and children of patients with nasopharyngeal carcinoma (NPC) and patients with NPC who were randomised to have their nasopharynx examination and annual Epstein-Barr virus (EBV) serology. Serum titers or levels for EBV VCA IgA and EA+EBNA-1 IgA, the specificity reached as high as 99.2% and 95.1%, respectively, in the control groups. However, correlation of these three assays with clinical manifestations of NPC, revealed only EBV DNA load significantly associated with N stage and overall stage in NPC patients. Additionally, EBV DNA load could be used to further raise the specificity of EBV EA+EBNA-1 IgA assays. When comparing the 5cm and 10cm incision groups, there is no clinically significant difference in subjective patient satisfaction with their scar at any time point, using the patient and observer scar assessment scale. Objective assessment using the Vancouver scar scale also failed to find a clinically significant difference. In addition there is no difference in the post operative complication rate between the two groups. Conclusion: In thyroid surgery the length of the incision appears to have little effect on cosmetic outcomes when comparing a standard 10 cm incision with a minimally invasive 5 cm incision.

Results: After constructing the receiver operating characteristics to determine the viability of such a program. Material and Methods: Five hundred seventeen consecutive subjects, including 156 NPC patients, 264 healthy volunteers, and nineteen patients with head-and-neck squamous cell carcinoma (HNSCC) were enrolled. The sensitivity and specificity of EBV IgAs to viral capsid antigen (VCA), complementary EBV IgAs to early antigen and nuclear antigen-1 (EA+EBNA-1), and EBV DNA load were examined by immunofluorescent assays, enzyme-linked immunosorbent assays, and quantitative real-time PCR, respectively.

Results: After constructing the receiver operating characteristics to demonstrate screening efficacy, EBV EA+EBNA-1 IgA (AUC: 0.952; 95% CI, 0.930-0.974) was proved superior to EBV VCA IgA (AUC: 0.888; 95% CI, 0.854-0.922) or EBV DNA load (AUC: 0.893; 95% CI, 0.850-0.932) in differentiating NPC patients from controls. Comparison of screening efficacy between NPC patients and HNSCC patients revealed EBV EA+EBNA-1 IgA (AUC: 0.964; 95% CI, 0.943-0.985) still outperformed EBV VCA IgA (AUC: 0.884; 95% CI, 0.845-0.923). In subjects with higher serum titer or level equal to or above 1:60 and 6 EU/ml for EBV VCA IgA and EA+EBNA-1 IgA, the specificity reached as high as 99.2% and 95.1%, respectively, in the control groups. However, correlation of these three assays with clinical manifestations of NPC, revealed only EBV DNA load significantly associated with N stage and overall stage in NPC patients. Additionally, EBV DNA load could be used to further raise the specificity of EBV EA+EBNA-1 IgA assays. When comparing the 5cm and 10cm incision groups, there is no clinically significant difference in subjective patient satisfaction with their scar at any time point, using the patient and observer scar assessment scale. Objective assessment using the Vancouver scar scale also failed to find a clinically significant difference. In addition there is no difference in the post operative complication rate between the two groups. Conclusion: In thyroid surgery the length of the incision appears to have little effect on cosmetic outcomes when comparing a standard 10 cm incision with a minimally invasive 5 cm incision.

S119: COMPLEMENTARY SERUM TEST OF ANTIBODIES TO EBV EA+EBNA-1: A POSSIBLE ALTERNATIVE FOR PRIMARY SCREENING OF NPC

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Object: This hospital-based cohort study evaluated the efficacy of three Epstein-Barr virus (EBV) - associated assays for nasopharyngeal carcinoma (NPC) patients. Material and Methods: Five hundred seventeen consecutive subjects, including 156 NPC patients, 264 healthy volunteers, and nineteen patients with head-and-neck squamous cell carcinoma (HNSCC) were enrolled. The sensitivity and specificity of EBV IgAs to viral capsid antigen (VCA), complementary EBV IgAs to early antigen and nuclear antigen-1 (EA+EBNA-1), and EBV DNA load were examined by immunofluorescent assays, enzyme-linked immunosorbent assays, and quantitative real-time PCR, respectively.

Results: After constructing the receiver operating characteristics to demonstrate screening efficacy, EBV EA+EBNA-1 IgA (AUC: 0.952; 95% CI, 0.930-0.974) was proved superior to EBV VCA IgA (AUC: 0.888; 95% CI, 0.854-0.922) or EBV DNA load (AUC: 0.893; 95% CI, 0.850-0.932) in differentiating NPC patients from controls. Comparison of screening efficacy between NPC patients and HNSCC patients revealed EBV EA+EBNA-1 IgA (AUC: 0.964; 95% CI, 0.943-0.985) still outperformed EBV VCA IgA (AUC: 0.884; 95% CI, 0.845-0.923). In subjects with higher serum titer or level equal to or above 1:60 and 6 EU/ml for EBV VCA IgA and EA+EBNA-1 IgA, the specificity reached as high as 99.2% and 95.1%, respectively, in the control groups. However, correlation of these three assays with clinical manifestations of NPC, revealed only EBV DNA load significantly associated with N stage and overall stage in NPC patients. Additionally, EBV DNA load could be used to further raise the specificity of EBV EA+EBNA-1 IgA assays. When comparing the 5cm and 10cm incision groups, there is no clinically significant difference in subjective patient satisfaction with their scar at any time point, using the patient and observer scar assessment scale. Objective assessment using the Vancouver scar scale also failed to find a clinically significant difference. In addition there is no difference in the post operative complication rate between the two groups. Conclusion: In thyroid surgery the length of the incision appears to have little effect on cosmetic outcomes when comparing a standard 10 cm incision with a minimally invasive 5 cm incision.

S120: SEQUENTIAL DETECTION OF PLASMA EBV DNA LEVELS IN A COHORT OF HIGH RISK INDIVIDUALS FOR NASOPHARYNGEAL CARCINOMA

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Aim: Plasma EBV DNA has been reported to be raised in nasopharyngeal carcinoma (NPC) patients. Furthermore it is thought to be raised in recurrences even before any detectable disease clinically. Most of the plasma EBV DNA results reported have been one-off detection process. The objective of the study is to elucidate the potential of plasma EBV DNA copies and define its role in screening for NPC in high risk individuals. Material and Methods: A prospective cohort study was conducted in normal patients with a family history of NPC. Institutional review board approval was obtained. History taking and clinical examination, including flexible nasopharyngoscopy were performed. Any nasopharyngeal mass seen on examination was taken for biopsy even if it appeared like an adenoidal mass. Patients were followed up 6 monthly and serial plasma EBV DNA copies were sequentially taken at 0, 1, and 2 years. A separate
plasias, 1 moderate dysplasia, 1 CIS, 1 SCC and 1 SGC. Conclusion: Our results demonstrate that AFL visualization is very efficient in identifying pre-malignant and malignant oral lesions not detected with WL alone. This technique has the potential as a non-invasive and effective screening tool for oral cancers and pre-cancerous lesions.

S121: AUTOFLUORESCENCE LIGHT SCREENING FOR PRE-MALIGNANT AND MALIGNANT ORAL LESIONS

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Objective: To determine if autofluorescence light (AFL) visualization in addition to white light (WL) exam can increase the detection of pre-malignant and malignant lesions in the oral cavity of high risk patients.

Methods: Our study included 30 patients who visited the department of Dentistry and Head and Neck Surgery at Roswell Park Cancer Institute (RPCI), between September 2006 and July 2007, either for follow up of a previously treated head and neck cancer or by referral from community dentists to investigate suspicious oral lesions. The patients consented to the study and filled out a questionnaire regarding their health history and personal habits. The patients then underwent a comprehensive oral exam with an autofluorescence device which was equipped with WL source, an AFL source (light at 400-460nm) and a video camera. Suspicious lesions that were identified under the WL were retraced by AFL examination. At least one biopsy was obtained from every suspicious lesion detected by WL alone, AFL alone and both WL and AFL. One control biopsy was obtained per patient from a normal appearing area within the oral cavity, primarily from the contralateral side. The same dentist performed all examinations and biopsies. A total of 145 biopsies were obtained from the 30 patients (average of about 5 per person) and all were reviewed by the same pathologist.

Results: The pathologic diagnoses were grouped into four categories for convenience of analysis: (1)‘Normal’ - normal and parakeratosis without atypia; (2) ‘Initiated’ - parakeratosis with atypia, mild dysplasia with/without parakeratosis and atypia; (3) ‘Progressing’ - moderate or severe dysplasia; (4) ‘Cancers’ - in-situ carcinoma (CIS), squamous cell carcinoma (SCC), verrucaous carcinoma, salivary gland carcinoma (SGC). These groups contributed 45, 74, 12 and 14 biopsies respectively. Our results showed that while WL inspection missed 3 moderate/severe dysplasias, 1 CIS, 2 SCC and a SGC; AFL-aided inspection did not miss any lesions graded moderate dysplasia or worse. The WL alone was 50% sensitive in detecting the initiated lesions compared to a sensitivity of 70% with AFL alone. Sequential screening with WL and AFL together was 81% sensitive.

Conclusions: Our results demonstrated that sequential screening with WL and AFL together is superior to WL alone. Sequential screening with WL and AFL is recommended for high risk patients. Sequential screening with WL and AFL together detected more initiated lesions than WL alone.

S122: BETA-CAROTENE’S OXIDATIVE METABOLISM MAY REPRESENT A CANCER RISK WITH ONGOING TOBACCO USE

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Introduction: Carotenoids (i.e. alpha-, beta-carotene, lycopene, lutein, etc.) are bioactive food-based compounds thought to have great potential to protect against cancer development. Despite convincing epidemiologic and in-vitro evidence supporting the protective effects of carotenoids against tobacco-related cancer development, their true impact has been brought into question as a result of several recent clinical studies suggesting that carotenoids may act as a contributory causal risk for cancer development under the specific conditions of ongoing tobacco use. The difficulty in interpreting these studies is that carotenoid’s oxidant biology has not been adequately evaluated in specific tissues under various oxidative conditions. Utilizing a novel, non-invasive technology with which to determine carotenoid concentrations in-vitro and in-vivo, Raman Spectroscopy, previous work has demonstrated that head and neck cancer cell lines have less Raman detectable tissue carotenoids. We hypothesize that under conditions of high oxidative stress carotenoids undergo metabolism to byproducts less detectable by our clinical Raman instrument under the conditions of tobacco-induced oxidative stress. Materials and Methods: Raman spectroscopy was used to determine if supplementation of oral cavity cancer cell lines with beta-carotene increased the measurable Raman signal. Moreover, we determined if the Raman signal was found to decrease in beta-carotene supplemented cells after exposure to endogenous and exogenous oxidative stress. The breakdown of beta-carotene was confirmed by UV spectroscopy. Finally, we confirmed the breakdown of beta-carotene to oxidative breakdown products using high pressure liquid chromatography (HPLC). Results: Supplementation of our oral cavity cancer cell lines with beta-carotene increased the Raman signal. Moreover, the
S123: A TALE OF TWO SITES: CORRELATION OF HPV SUBTYPES IN HEAD AND NECK CANCER AND CERVIX IN WEST VIRGINIA

Objective: Increasingly, high-risk human papilloma virus (HPV) is found to be associated with a subset of head and neck cancers. West Virginia has a relatively high incidence of squamous cell carcinoma of the head and neck as well as cervical cancer in women. We reviewed data from two studies: one analyzing HPV subtypes in the oral cavity in patients with known head and neck cancer and the other a screening study for HPV prevalence in indigent Appalachian women. We compared the prevalence of various less commonly reported HPV subtypes (those other than 16 and 18) to determine whether similar subtypes were found between these populations. Such a correlation would help support the concept that HPV related head and neck cancer is a sexually transmitted disease and that other subtypes must be considered when developing vaccines.

Methods: There were 227 patients in the head and neck study and all of these patients had a primary head and neck cancer: oral, pharyngeal, laryngeal or those with unknown primary sites. These patients were screened for high-risk HPV using a cytology brush technique to obtain oral exfoliated cells. Those found to be HPV positive had genotyping performed by PCR. These results were compared to 158 patients from a group of 878 Appalachian women who had previously been screened for HPV, using a similar technique for obtaining cells and a combination of signal amplification (Hybrid Capture II) and PCR.

Results: In total, 36 patients (16%) in the head and neck group as compared to 158 patients from a group of 878 Appalachian women who had previously been screened for HPV, using a similar technique for obtaining cells and a combination of signal amplification (Hybrid Capture II) and PCR. HPV 39 was identified in 6.3%, HPV 51 in 12.7%, both much higher than the expected 22% vs. 19% and 8%. In the cervix of the women screened, HPV 39 was identified in 12.7% HPV 18 in 12.7% and HPV 16 in 4.4%. Other HPV subtypes were less common.

Conclusions: These results would suggest that similar genotypes are found in the squamous mucosa of the head and neck and the cervix in our population of rural, Appalachian patients. Obviously, we surveyed different populations with different study designs. Nevertheless, the high prevalence of HPV types 39 and 51 is a striking finding and would appear to support the hypothesis that oral sex behavior correlates with HPV related head and neck cancers. Clearly, further study should help to elucidate the epidemiology and pathogenesis of HPV infection as well as carcinogenesis in this population. Furthermore, this will help refine vaccination strategy in this region.

S124: CIGARETTE SMOKE REGULATES REACTIVE OXYGEN SPECIES METABOLISM IN THE LARYNX

Objective: Cigarette smoke contains over 4000 compounds, many of which promote oxidative damage. In the lower airway, smoke-induced free radicals have been associated with degenerative pulmonary diseases and cancer. Recently, cigarette smoke has been shown to increase reactive oxygen species (ROS) in the larynx in a mouse model. We seek to expand these preliminary findings to the analysis of human tissue as well as the effects of cigarette smoke condensate on laryngeal fibroblasts in vitro. We hypothesize that alterations in the laryngeal tissue phenotype associated with prolonged tobacco exposure are regulated through free radical induction and their downstream effects on mesenchymal cells. Therefore, we seek to provide preliminary data regarding the effects of cigarette smoke on ROS metabolism and gene regulation in human laryngeal tissue as well as a laryngeal fibroblast cell line.

Methods: Human vocal fold mucosa collected during phonomicrosurgical resection of benign vocal fold lesions (vocal fold polyps and Reinke’s edema) was harvested from current and never smokers. This tissue was subjected to analyses for genes related to oxidative stress, hemeoxygenase-1 (HO-1) and superoxide dismutase (SOD1). In addition, we characterized the oxidative stress response to cigarette smoke condensate (CSC) at doses of 10, 50 and 100 lg/mL. Dichlorofluorescin (DCF) derivatives were quantified in response to CSC as well as the expression of ROS-related genes. In addition, the effects of CSC on fibroblast migration and apoptosis were determined using standardized in vitro methods.

Results: Both HO1 and SOD1 gene expression was significantly increased in vocal fold mucosa from current smokers compared to never smokers. Furthermore, gene expression patterns differed between current smokers with Reinke’s Edema versus current smokers with an isolated polyp. In vitro, CSC mediated a dose-dependent increase in intracellular H2O2, determined by DCF, as well as HO1 and SOD1 gene induction in human vocal fold fibroblasts. Exogenous CSC also decreased fibroblast migration and increased fibroblast apoptosis in a dose-dependent fashion.

Conclusions: Cigarette smoke increases free radical synthesis in human vocal fold mucosa and is likely a contributor to the inherent alterations in tissue phenotype in many smokers through its regulation of multiple mesenchymal cell activities. Increased insight into these processes may prove useful in establishing the underlying mechanisms by which smokers typically develop pathological conditions of the larynx ranging from Reinke’s Edema to carcinoma, and provide appropriate therapeutic targets for disease prevention and treatment.
To review the indications and limitations of endoscopic dural repair, we conducted a retrospective study of 70 cranial base cases from April 1996 to 2007. The neural crest cells of the autonomic nervous system, familial PGL have recently been shown to be associated with germline alterations in succinate dehydrogenase genes (SDHB, SDHC and SDHD), and occasionally with genes known from the multistepic disorders Von Hippel-Lindau disease (VHL) and Multiple Endocrine Neoplasia type 2 (MEN2). However, SDH mutations also appear in 8-25% of sporadic patients that in fact may be occult familial cases. Little is known about the genetic changes involved in the tumor development of PGL. The aim of this study was to compare DNA copy number changes in tumors of familial and sporadic cases. Methods: This study included 8 familial and 16 sporadic patients with benign head and neck PGL (carotid body, tympanic, yugular and vagal). Using DNA extracted from peripheral blood lymphocytes we analyzed germline mutations in SDHx, VHL and RET by direct sequencing and possible exon deletions in SDHx, VHL and RET. The choice of materials used for dural repair, postoperative management of sino-nasal malignancies have undoubtedly contributed to extend the indications of this approach. EDR was a safe procedure with an acceptable complication rate, which allows a wide resection of anterior skull base dura and consequently a correct histologic assessment of its involvement. This information can help in defining the need for adjuvant treatment. The surgeon must be able to intraoperatively switch to an external frontal craniotomy whenever the intraoperative assessment of tumor extent suggests that resection within safe margins and proper duraplasty cannot be performed through a pure endoscopic approach.

**Clinical: Skull Base I**

**S127: Endoscopic Dural Resection in the Management of Selected Sino-Nasal Malignancies: Surgical Technique and Morbidity**

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**Objective:** To review the indications and limitations of endoscopic dural resection (EDR) and repair in the management of selected sino-nasal malignancies. Surgical technique, technical pointers to optimize the results, evolution in EDR by MPR, microsurgeon’s experience was comparative DNA analysis, and complications are discussed. **Methods:** From April 1996 to November 2007, 159 patients affected by malignant tumors of the sino-nasal tract were treated by pure endoscopic resection at two referral University Hospitals. Starting from 2004, 35 patients were submitted to EDR, i.e. antero-posteriorly from the posteroinferior wall of frontal sinus to the planum sphenoidale and lateral to the lamina papyracea (unilateral resection, N=24) or between the two laminae papyraceae (bilateral resection, N=11). Whenever extensive macroscopic dural involvement, a lateral extension in close proximity to the orbital roof, or involvement of the anterior wall and lateral portion of the frontal sinus was detected, the endoscopic approach was coupled with a subfrontal craniotomy to obtain better exposure of the lesion from above. The choice of reconstruction materials has gradually shifted towards autologous tissues. Duraplasty with a 3-layer technique was preferably carried out using fascia lata for the intracranial intradural and extradural layers (underlay), and nasal mucoperiosteum obtained from the contralateral nasal fossa (when available) or a third piece of fascia lata for the extracranial layer (overlay). All patients received an intravenous blood-brain barrier crossing antibiotic for the intracranial intradural and extradural layers (underlay), and nasal mucoperiosteum obtained from the contralateral nasal fossa (when available) or a third piece of fascia lata for the extracranial layer (overlay). The resected dura was involved by the tumor in 7 (20%) cases (3 adenocarcinomas, 3 ONBs, 1 fibrosarcoma). Overall, 16 (46%) patients received adjuvant treatment. After a mean follow-up of 16 months (range, 1-41), 34 (97%) patients had no evidence of disease. One patient has asymptomatic persistent disease after surgery and is currently undergoing adjuvant radiotherapy. **Conclusions:** The improvement of surgical instrumentation and the experience acquired during an 11-year period in the endoscopic management of sino-nasal malignancies have undoubtedly contributed to extend the indications of this approach. EDR is a safe procedure with an acceptable complication rate, which allows a wide resection of anterior skull base dura and consequently a correct histologic assessment of its involvement. This information can help in defining the need for adjuvant treatment. The surgeon should be able to intraoperatively switch to an external frontal craniotomy whenever the intraoperative assessment of tumor extent suggests that resection within safe margins and proper duraplasty cannot be performed through a pure endoscopic approach.

**S128: Navigated Control: Autopilot Assistance for Surgical Dissection in Skull Base Malignancies**


**Objective:** Navigated-controlled instruments permit a preoperative programming of the resection volume, the borders and the surgical approach of skull base malignancies, and are able to determine the optimal navigation taking advantage of patient models from CT. The intraoperative navigation of the current parameters is realized by the action of guided instrument (surgical drill, shaver) on the basis of the current X-Y-Z-coordinates. Therefore a precise and durable navigation of the instrument is necessary. **Methods:** The navigated control system consists of a surgery engine, an opto-electric navigation system and a processor unit. Altogether 44 patients were accomplished in the period 2006 to 12.07. Approaches at the lateral skull base (14 x mastoidectomy, 1 x extended mastoidectomy) and the lateral skull base (27 transnasal, 2 transanatal approaches) were documented. Time, movement of the surgical drill and shaver, ergonomic parameters of the surgeon and a questioning to the ergonomic characteristics of the system were recorded. **Results:** 42 of 42 surgeries could be completed successfully with the autopilot-system. The maximum calculated deviation of the registration amounted to 0.91 mm. In no case a defined risk structure has been damaged. The time was not significantly changed in relation to the gold standard. The system was estimated as reliable by the users. A steep learning curve and an increasing confidence could be determined into the correct function of the system. **Conclusions:** This study proves the clinical operability of navigated-controlled instruments for the skull base surgery. Improvements are necessary in the range of work space planning and the registration of the patient.
removed and avoidance of surrounding structures. The sensitivity, specificity, positive and negative predictive values, and variability for each task were measured as a function of scan angle, and qualitative feedback regarding imaging performance and the effect on surgical decision making was obtained. Results: Intraoperative tomosynthesis quantitatively provided reduced imaging time and radiation dose - each linear with acquisition arc (1.5 sec, 2.5 mGy for 60º vs. 60 sec, 9.7 mGy for 178º). Image quality depended heavily on arc - suprasellar lesions (arc <60º) image quality was severely limited by out-of-plane blur (distortion), while arcs >90º provided acceptable image quality for guidance of most tasks. Full cone-beam CT (~180º arc) provided accurate, sub-mm-3D soft-tissue structures visualization. Surgical performance improved with tomosynthesis arc, depending on the task. While simple tasks (e.g., uncinectomy) exhibited little dependence on acquisition arc, more challenging tasks (e.g., olivary ablation) demonstrated a steeper dependence of performance on arc, both qualitatively (sensitivity and specificity) and qualitatively (surgical confidence and satisfaction with surgical product). The sensitivity in target ablation improved from 42.1% at an arc of 20º, to 59.5% at 60º, and 77.1% at 180º (cone-beam CT). Surgical confidence was improved in all cases, with intraoperative tomosynthesis providing direct, near real-time confirmation of surgical approach, particularly in relation to abnormal anatomy and challenging ablation tasks. Conclusion: Intraoperative tomosynthesis provides the surgeon with up-to-date images of the target and related structures, overcoming limitations associated with pre-operative image guidance. The images can be obtained intra-operatively in less than ~30 seconds, with a radiation dose dose equivalent to ~1/10 of a typical diagnostic CT or less. The technology provided quantifiable benefits to the surgeon facilitating total target ablation, helping to spare surrounding vital structures, and improving the quality of surgical product. Tomosynthesis is clearly a useful complement to existing imaging modalities. The combination allows high-quality images to be augmented by fast, repeat tomosynthesis images acquired at any point within the procedure.

S130: LONG TERM FOLLOW-UP OF PROTON BEAM RADIATION THERAPY FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE PARANASAL SINUSES: A 10-YEAR EXPERIENCE

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Purpose: To evaluate the treatment outcome in patients with locally advanced squamous cell carcinomas (SCC) of the paranasal sinus with highly conformal proton radiotherapy (RT) and surgery. To determine potential prognostic factors which affect survival. Materials/Methods: Between 1991 and 2005, 51 patients with locally advanced (T3-4) non-metastatic paranasal sinus SCCs received 3-D conformal proton RT at the Massachusetts General Hospital. The median age was 56 (range, 17 - 82). The median Karnofsky Performance Status, (KPS) was 90. The primary tumor location included the maxillary sinus in 21, ethmoid sinus in 9, nasal cavity in 8, sphenoide sinus in 10, and frontal sinus in 3 patients. Thirty-five percent of patients underwent a gross total resection (GTR) prior to RT. Twelve patients (24%) underwent craniofacial resection (CFR), 26 (51%) underwent transfacial resection (TFR), and the remaining 13 (25%) patients underwent biopsy only. The median total radiation dose to the primary tumor volume was 72 Gray over 44 days. Twenty-five percent of patients received cisplatin based concurrent chemoradiation. The median follow-up of all living patients was 48 months. Results: As the first site of failure, 7, 7 and 12 patients developed local, regional, and distant metastasis, respectively. Of the distant recurrences, 6 were leptomeningeal and 6 were systemic. The 3-year actuarial rates of local, regional, and freedom from distant metastasis were 76%, 82%, and 72%, respectively. The 5-year disease-free (DFS) and overall survival (OS) rates at 3 years were 37% and 52%, respectively. In multivariate analysis, a higher KPS score, a GTR with negative margins and a higher percentage of protons (70% or more) were significant for predicting improved OS (Table 1). Concurrent chemotherapy appeared to have a trend in improved OS at 2 years (82% vs. 55%), however this was no longer seen at 3 year follow-up. Complications from combined therapy included 6 patients with CFR, who developed Common Toxicity Criteria (CTC) grade 4 soft tissue fibrosis requiring revision surgery, 1 patient required orbital exenteration secondary to plate extrusion, 2 patients developed MR detected asymptomatic cerebral radiation change, and 1 patient developed osteomyelitis of the skull base. There were no CTC grade 3-5 visual/ocular radiation induced toxicities. Conclusions: Combined modality therapy with definitive radiotherapy and surgery provides promising results in a promising local control and survival for patients with locally advanced SCC of the paranasal sinus, with acceptable toxicity.

S131: CLINICAL OUTCOMES OF SINONASAL CANCERS TREATED WITH ENDOSCOPIC ENDOANALYSIS RESECTION

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Objectives: To understand the principles and limitations of complete endoscopic resections of sinonasal cancers and be able to relate these to patient outcomes. We stress the importance of a complete anatomic resection, intraoperative margins and the need to convert to open procedures to clear tumor margins if needed. Methods: Retrospective analysis of all sinonasal cancer patients treated endoscopically for cure at our Cranial Base Center. Results: Seventy patients underwent endoscopic resections of sinonasal cancers with curative intent with at least 12 months of follow-up or recurrence. Mean follow-up was 34 months. Four patients underwent conversion to an open procedure to clear tumor margins. The majority of tumors were squamous cell carcinoma, adenoid cystic carcinoma, esthesioneuroblastoma and nasopharyngeal carcinomas. Rare tumors included were adenocarcinoma, melanomas, rhododomyosarcomas, sinonasal undifferentiated carcinomas, and hemangiopericytomas. Perioperative complications were noted in 22 patients with no perioperative deaths. Of the patients with endoscopic dural resections, 16% had post operative CSF leaks; however, since the utilization of the pedicled nasoseptal flap this has fallen to 6%. One and three year disease free survival rates were 84% and 71% respectively. Eighty percent of patients underwent adjunctive radiotherapy. Patients with negative pathologic margins had significantly better disease free survival than those without (p<0.02). Conclusions: For appropriately selected sinonasal cancer patients, endoscopic endonasal resection provides very good disease free survival and acceptable morbidity. The importance of a truly endoscopic oncologic resection with clear margins is of paramount importance and the conversion to an open resection is needed in 6% of patients.

S132: TREATMENT OF ESTHESIONEUROBLASTOMA WITH ENDOANALYSIS CRANIAL BASE RESECTION

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Objectives: To understand the principles and limitations of complete endoscopic resections of esthesioneuroblastoma including endoscopic dural and olfactory nerve resections and endoscopic reconstruction. We stress the importance of a complete anatomic resection, intraoperative margins and the need to convert to open procedures to clear tumor margins if needed. Methods: Retrospective analysis of all esthesioneuroblastoma patients treated endoscopically for cure. Results: Seventeen patients underwent endoscopic resections of esthesioneuroblastoma with curative intent. The exophytic brainstem and cranial base resection includes anterior and posterior ethmoidectomies, and exposure of the nasofractral recesses, exposure the paramedian anterior skull base including the fovea ethmoidalis, the vertical and horizontal lamellae of the cribiform plate and its olfactory fila, and the anterior and posterior ethmoidal artery canals. A Draf III or endoscopic Lothrop procedure exposes the posterior wall of the frontal sinus and enhances the exposure of the anterior margin of the tumor. The orbital lamellae are resected for margins and medial maxillectomies are performed if needed. The dura, olfactory nerves and intracranial tumor are resected. The skull base defect is reconstructed with either a nasoseptal flap if available or an inlay/onlay reconstruction with Alloderm. Mean follow-up was 31 months. 13 of 17 patients underwent adjunctive radiotherapy. Sixteen of 17 patients had no evidence of disease at the last follow-up. Three of 17 patients had post operative CSF leaks but all were repaired with endoscopy revision skull base reconstruction. Conclusions: For appropriately selected esthesioneuroblastoma patients, endoscopic cranial base resection as a part of multimodal treatment regimen provides excellent disease free survival and acceptable morbidity. Sixteen of 17 patients were disease free at last follow-up.

S133: A PROSPECTIVE EVALUATION OF THE SHORT-TERM IMPACT AND RECOVERY OF QUALITY OF LIFE AFTER ANTERIOR SKULL BASE SURGERY

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Objective: Technical developments in the fields of head and neck surgery and neurosurgery have had a major impact on the long-term survival of patients with skull base tumors. However, the physical and psychological sequelae of surgery and its impact on patient’s quality of life (QOL) have not been prospectively evaluated. The purpose of this study was to evaluate
the health-related QOL of patients, before and after surgery for anterior skull base tumors. Methods: Demographic, medical and outcome data on 35 patients undergoing subcranial surgery for extirpation of tumors were analyzed. The Anterior Skull Base Surgery (ASBS) QOL Questionnaire, a disease-specific instrument developed for this population, was utilized. All patients completed the ASBS-QOL questionnaire before surgery, and 6 and 12 months after the operation. Results: Compared to the QOL scores reported before surgery, there were significant decreases in the physical functioning domain scores (from 4.2±0.9 to 3.6±1.0, P<0.004) and specific symptoms domain scores (from 3.9±0.9 to 3.4±1.1, P<0.04) 6 months after surgery. Histology and radiotherapy had significant impact on overall QOL (P<0.04). Malignant tumors and adjuvant radiation therapy were associated with significantly poorer scores in the physical functioning (33% decrease, P<0.004), role of performance (26% decrease, P<0.03), vitality (26% decrease, P<0.006) and specific symptoms domains (32% decrease, P<0.004). In contrast, surgery improved the QOL scores of patients with benign tumors, most significantly in the impact upon emotion domain (20% increase, P<0.004). When QOL was estimated 12 months after surgery, the overall health-related QOL scores improved, and were not statistically different from those reported before surgery (P<0.04). Conclusion: Our prospective study shows that the overall QOL of patients after anterior skull base tumor resection is preserved within the first year after surgery. Histology and radiotherapy are significant predictors of health-related QOL in this population. This study further validates the ASBS-QOL questionnaire as an appropriate instrument for estimation of health related quality of life in this population.

S134: SURGICAL TECHNIQUE OF “FACIAL DISMASKING APPROACH” FOR CRANIOFACIAL LESION S. Kishimoto1, A. Tsunoda1, H. Koda1, 1Tokyo Medical and Dental University, Tokyo, Japan

Objective: Surgery of the central skull base is difficult, because of the complicated facial skeleton and the depth of the surgical field. In order to access this area, wide exposure of the facial skin flap with long facial skin incision is necessary, which results in formation of striking facial scars and injury of the facial nerve. To avoid such scars and facial nerve palsy, we employed the facial dismasking approach (Laryngoscope 117(9):1533-1538, 2007). This presentation is aimed at demonstration of the new surgical technique of the facial dismasking approach for craniofacial lesions, using video. Surgical Technique: The facial dismasking flap is a combination of a coronal skin incision and a circumpalpebral incision. By adding a circumpalpebral incision, the skin can be detached from the orbital structures and the coronal skin flap can be elevated more inferiorly together with the facial nerves and muscles. In order to preserve the function of eyelid opening and closure, the superficial structures above the septum orbitale and tarsus should be carefully elevated. Result: Twenty-three patients with tumors in various locations such as the maxillary sinus, paranasal sinus, zygoma and infratemporal fossa, who had undergone a facial dismasking flap, were studied. Sufficient surgical fields were obtained for removal of the tumor in all patients. Tumors were totally resected in 21 patients and were subtotally resected in two patients to avoid optic nerve damage. Facial nerves were anatomically preserved and facial scarring was minimal in all patients. No facial palsy or eyelid dysfunction was found in any patients. Conclusion: The facial dismasking flap widely exposes up to the upper two-thirds of the facial skull. Furthermore, it fully preserves facial and eyelid movement and minimizes scarring. From our experience, this flap is useful for en bloc resection of tumors in the skull base or craniofacial lesions.

S135: ADVANTAGES AND OUTCOMES OF FREE TISSUE TRANSFER FOR DEFECTS OF THE SCALP AND LATENT TEMPORAL BONE M. S. Teng1, E. M. Ngdee2, N. D. F. Tran3, 1Mount Sinai Medical Center, New York, NY; 2University of Washington, Seattle, WA

Objectives: Defects of the scalp and latent temporal bone may result from tumor, trauma, or chronic infection. The specific goals of reconstructing these defects are to restore the bony contour, soft tissue thickness, and epithelial coverage to the area, and seal intracranial contents. It is important to create a durable tissue which withstands trauma or radiation, and heals relatively quickly to allow for any necessary adjuvant therapies to be administered in a timely fashion. Simple reconstructive methods such as skin grafts, locoregional flaps, or tissue expanders are often infeasible because of defect size, active infection, radiation, or dural exposure. Pedicled flaps also have limited reach to the defect due to the length of the vascular pedicle. Because of these considerations, and the anatomic challenges of this region of the body, free tissue transfer is particularly useful, and commonly necessary, in scalp and latent temporal bone reconstruction. We present our use of microvascular reconstructive techniques in managing these defects. Methods: Data were collected on all patients at the University of Washington Medical Center who had scalp or latent temporal bone defects reconstructed with free tissue transfer from May 1996 - September 2007. Cases were analyzed for defect characteristics, type of flap, vessel selection, radiation status, dural exposure, complications, and outcomes. Results: During the study period, 54 free flaps were performed in 51 patients with scalp or latent temporal bone defects. Indications for surgery were diverse: a variety of malignant neoplasms (40), chronic wound/ORN/osteomyelitis (14). Thirty-seven defects were located on the scalp, and 14 on the latent temporal bone. Fourteen resections included cranectomy. Cranial bone grafts, titanium mesh, or porous polyethylene implant (Paprosky Surgical Inc., Neenah, GA) were used as cranial cavity materials. The latter method was utilized for the most recent nine cases. 38 patients had either pre- or postoperative radiation. Defect size ranged from 6-550 cm2 with a mean of 14.4±cm2. All flaps (35 latissimus, 11 rectus, 3 radial forearm, 4 anterolateral thigh, and 1 omental) were transferred successfully. Vein grafts were required in only three cases. Follow-up ranged from 3 months to 8.5 years (mean: 3 years). Major complications occurred: cerebritis with seizures, large wound dehiscence, abdominal wound hematoma, and skull osteomyelitis. Eight minor complications consisted of three wound dehiscences which healed with conservative management, and six seromas in latissimus dorsi donor site wounds, representing 17.1% of the latissimus flaps in the series. Cosmetic results were consistent and durable. Conclusion: Microvascular free tissue transfer is a safe, reliable method for reconstructing defects of the scalp and latent temporal bone defects while offering favorable cosmetic results. Major complication rates are low. We favor the use of latissimus dorsi muscle-only flap with meshed skin graft coverage for large scalp defects for its most ideal contour, color match and long pedicle length. When calvarial defects are present, custom porous polyethylene implants are well tolerated beneath the flap. Bulker flaps such as the anterolateral thigh and latissimus dorsi free flap are more appropriate for lateral temporal bone defects.

BASIC SCIENCE: OTHER

S136: DNA DOUBLE STRANDED BREAK REPAIR MECHANISMS IN ORAL CARCINOMAS FROM YOUNG AND OLDER PATIENTS P.L. Boehr1, P. Pintor dos Reis1, J. Machado1, R. Bharadwaj1, R. Grénman2, P. Gullane3, J. Irish4, V. D. Silva2, S. Kamel-Reid1, 1Applied Molecular Oncology, Ontario Cancer Institute and University Health Network, Toronto, ON, Canada; 2Otorhinolaryngology/Head and Neck Surgery, and Biochemistry, Turku University C, Turku, Finland; 3Otorhinolaryngology and Surgical Oncology, Princess Margaret Hospital, Toronto, ON, Canada; 4Otorhinolaryngology and Surgical Oncology, Princess Margaret Hospital, Toronto, ON, Canada; 2Pontificia Universidad Catolica do RS, Porto Alegre, Brazil

Objectives: To gain further insight into DNA repair mechanisms in oral squamous cell carcinoma (OSCC) from young and older patients. Our main goal was to determine if DNA double stranded breaks (DSBs) are repaired in a different way in young versus older patients. We examined the ability to repair double stranded breaks (DSBs) by both Homologous Recombination (HR) and Non-homologous End Joining (NHEJ). Methods: We functionally assessed double stranded breaks using UT-SCC cell lines established from young (under 45 yr.) and older (over 45 yr.) patients. We examined global DNA damage by the Comet assay, to measure the degree of DNA fragmentation. Cells were irradiated (20 Gy), and collected at different time points. After electrophoresis, cells were stained with ethidium bromide, and observed under a fluorescent microscope. A total of 200 cells per sample were analyzed using the Comet image analysis system. HR and NHEJ analyses were performed using a plasmid-based repair assay, to measure the ability of the UT-SCC cell lines undergo DNA DSB repair. Results: In order to assess global DNA DSB repair, three independent assays were performed. All cell lines using the Comet assay, and no differences between lines derived from young and old patients were detected. When comparing irradiated vs. non-irradiated cells, we observed that both young and older cell lines are able to repair DNA DSBs caused by ionizing radiation after 24 hrs of exposure. To test whether there is deficien- cy or compensation from one DSB mechanism, we are currently analyz-
ing UT-SCC cell lines from young and older patients using HR and NHEJ assays. Conclusions: Our preliminary findings show that UT-SCC cell lines from both young and older patients are able to repair DSBs. As defects in one mechanism may be masked by adequate activity using another repair pathway, we are currently assessing DSB repair ability in cell lines from young and older patients using both HR and NHEJ assays.

S137: SALIVARY TRANSCRIPTOMES AS POTENTIAL EARLY DETECTION BIOMARKERS FOR ORAL CANCER A. Suresh, M. Vannan, J. E. M. Elango, F. A. Chen, Z. H. Ye, R. Glickman, M. Kuriakose, A. Amrita Institute of Medical Sciences, Cochin, Kerala, India; 2NYU Dental School, New York, NY; 3Amrita Institute of Medical Sciences, Cochin, Kerala, India

Objectives: To identify transcriptomes from saliva in patients with early stage oral cancer and precursor lesions which may serve as potential markers for early detection. Background: Early detection of oral cancer not only improve cure rates but also lowers morbidity of the treatment. Transcripts in human saliva may serve as potential non-invasive biomarkers for early detection of oral malignancies. Materials and Methods: Unstimulated saliva from 10 patients with early stage (T1/T2) Oral Squamous cell carcinoma and Pre-malignant lesions (PM) and 5 healthy volunteers were collected. Human saliva-derived mRNA was isolated and the quality of cell free mRNA was evaluated in this study with housekeeping genes such as Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and b-actin. The utility of salivary transcripts as biomarkers of oral cancer was investigated by quantifying the presence of 10 genes identified as over-expressed in a previous oral cancer cDNA microarray study. The expression profile in saliva was compared with tissue samples by Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). We confirmed the specificity of transcripts and the amplicons obtained from the cell free samples by sequencing of the RT-PCR products and by qRT-PCR, with and without DNAse treatment, using primers for the human housekeeping gene- GAPDH. Possibility of contamination with genomic DNA was confirmed the specificity of transcripts and the amplicons obtained from the cell free samples by sequencing of the RT-PCR products and by qRT-PCR, with and without DNAse treatment, using primers for the human housekeeping gene- GAPDH. Possibility of contamination with genomic DNA was further ruled out using rationally designed specific primers whose PCR products from mRNA and genomic DNA vary in size due to the splicing of introns. RT-PCR using GAPDH and Actin primers were done to check the integrity and quantity of the mRNA. The samples that conceded to these criteria were further analyzed for the expression of the target genes. The expression of head and neck cancer associated genes such as Matrix Metalloproteinase 1 (MMP1), Fibroblast Activation Protein, Alpha (FAP), Fibronectin 1 (FN1), Serine protease inhibitor, clade H (SERPINH2) and Interleukin 1B (IL1B) were analyzed in the samples by both RT-PCR and by qRT-PCR. Results: All the five genes were detected in the patients with T1/T2 cancer and with PMs while three (MMP1, SERPINH2, IL1B) were detected in the normal samples also. Expression of these genes was also analyzed in 5 paired tissue samples from oral cancer patients by Relative Quantification (Ct) comparative analysis. The expression profiles compared to that obtained in the different groups of saliva. Our study thus confirmed that transcripts in saliva, though degraded, could be detected by reverse transcription PCR and qPCR. Though bacterial transcripts are also present, the use of primers specific to the human genes, particularly to their splice junctions, will rule out the possibility of amplification from the genomic/bacterial transcripts. Conclusions: The detection of cancer associated transcripts by RT-PCR as well as by qRT-PCR in the saliva of oral cancer patients clearly pointed out to their utility as potential diagnostic markers of oral cancer. A comprehensive prospective study in a larger number of patients needs to be done in order to evaluate the efficacy and utility of these biomarkers.

S138: BIOLOGIC EFFECTS OF BONE MORPHOGENETIC PROTEINS ON ORAL CARCINOMA CELL LINES G. Zhou, M. Zhou, J. Xie, S. A. Jasser, J. N. Myers, MD Anderson Cancer Center, Houston, TX

Objective: To determine the efficacy of bone morphogenetic protein (BMP) treatments in oral carcinoma cell lines. Background: BMPs are bone morphogenetic protein receptors expressed in oral carcinoma cells that mediate the BMP-signaling pathway in representative oral carcinoma cell lines, and determine the in vivo biologic effects of these chronic BMP treatments in an orthotopic animal model for oral cancer. Methods: The oral squamous cell carcinoma (SCC) cell lines UMSCC-1 (floor of mouth) and UMSCC-74A (tongue) were studied. RT-PCR was used to determine baseline gene expression of BMPs, BMP-receptors (BMPRs), and key intracellular signaling pathway intermediates (Smads). An already well established nude mouse model for oral cancer was used for the in vivo experiments. There were 6 treatment groups for each cell line prior to inoculation to the animals in the in vivo models: (1) saline control; (2) rhBMP-2 at 100 ng/ml for 48 hours; (3) rhBMP-7 at 100 ng/ml for 48 hours; (4) Ad- BMP-2, (5) Ad- BMP-7, and (6) Ad-lacZ. Tumors were harvested and evaluated both grossly and histologically. Results: RT-PCR analysis revealed baseline gene expression of BMP-2 and BMP-7 in UMSCC-74A but not in the UMSCC-1 cell line. Both cell lines expressed all BMPRs and BMP-related Smads. Tumors derived from UMSCC-1 treated with rhBMP-2 or rhBMP-7 demonstrated no significant differences in tumor growth as compared to controls. Similarly, there was no change in tumor growth when UMSCC-1 was genetically modified by adenoviral transduction to express BMP-7, although tumor growth was significantly decreased when this cell line was transduced with Ad-BMP2. In contrast, tumors derived from UMSCC-74A treated with rhBMP-2, rhBMP-7, or Ad-BMP2 all resulted in significantly more aggressive tumor growth. The histology of these tumors also changed from an epithelial to a mesenchymal morphology. Tumors established from Ad-BMP7 transduced UMSCC-74A cells also showed rare areas of mature bone growth within the tumors. Conclusions: Oral carcinoma cell lines frequently express all the necessary components of the BMP-signaling pathway, and this pathway is functional as shown by the in vivo effects of these molecules on these cell lines in orthotopic animal models. In conclusion, the baseline expression of the BMPs may influence the biologic effects of stimulating this signaling pathway. The histologic changes observed for UMSCC-74A treated cells suggest that the BMP-pathway might have a role in regulating epithelial-mesenchymal transition in oral carcinoma, and there may be capacity for cellular plasticity in these cells.

S139: GAIN OF FUNCTION OF P53 MUTATIONS DISRUPT THE ATM-MEDIATED DNA DAMAGE RESPONSE IN HNSCC CELL LINES G. Zhou, M. Zhou, J. Xie, S. A. Jasser, J. N. Myers, MD Anderson Cancer Center, Houston, TX

Tp53 is the most commonly mutated tumor-suppressor gene in human tumors including head and neck squamous cell carcinoma (HNSCC). In addition to the loss of tumor-suppression function of wild type p53 by mutations, it is becoming increasingly clear that some mutant p53 proteins gain oncogenic properties favoring the development and progression of malignant tumors. Here, we report identification of one missense point mutation (R151S) and one c-terminal truncation mutation (delta 336) of p53 in HNSCC cell lines. To investigate their functional roles, we used lentiviral and retroviral expression systems to overexpress and suppress expression of these mutants in different HNSCC cell lines. Our results demonstrate that both these p53 mutants inhibit the Mre11-Rad50-NBS1 complex activation after DNA double-strand breaks (DSB) damage. Further analyses indicate that both these mutants inhibit the Mre11- Rad50-NBS1 complex activation after DNA double-strand breaks (DSB), leading to subsequent impaired Ataxia-telangiectasia mutated (ATM) activation. These results suggest an important role of these p53 mutants in inducing genomic instability and promoting tumorigenesis by actively disrupting ATM-mediated cellular responses to DNA DSB damage. In addition, since induction of DSBs is one of the important mechanisms involved in chemotherapy and radiotherapy of cancer cells, our findings are of great implication in understanding therapeutic resistance as well as treating HNSCC that express these p53 mutants.

S140: RADIATION INDUCES REACTIVE OXYGEN SPECIES METABOLISM AND FIBROTIC GENE EXPRESSION IN LARYNGEAL FIBROBLASTS B. E. Saltman, R. C. Branski, D. Felsen, D. P. Poppas, H. Szeto, D. H. Kraus, Memorial Sloan-Kettering Cancer Center, New York, NY; 2Memorial Sloan-Kettering Cancer Center, New York; 3Weill Medical College of Cornell University, New York

Objective: Radiation therapy (RT) has become one of the mainstays of head and neck cancer treatment. Although RT has been shown to be effective at oncologic control of many head and neck cancers, damage to the surrounding tissue results in significant morbidity. This morbidity is due to fibrosis affecting speech, voice and/or swallowing function. This intense fibrotic response has been shown to be mediated primarily through the actions of transforming growth factor beta (TGF-β) on mesenchymal cells. However, the underlying mechanism(s) associated with TGF-β induction are unclear. It is hypothesized that RT-induced fibrosis is mediated through reactive oxygen species (ROS) metabolism as well as direct effects on pro-fibrotic metabolism. This results in accumulation of ROS, which has been shown to be a critical step in RT-induced fibrosis.
ic gene transcription in mesenchymal cells. The current study seeks to address this hypothesis via an established in vitro model of radiation on an immortalized human laryngeal fibroblast cell line. Improved insight into the underlying pathophysiology of radiation-induced fibrosis is likely to provide targeted therapies to prevent and/or treat the significant morbidity associated with radiation-based cancer therapy. Methods: Normal human laryngeal fibroblasts (HVOX) were subjected to radiation at doses of 5, 10 and 20 Gray (Gy). At various timepoints after radiation exposure, the cells were subjected to analysis of ROS metabolism as well as pro-fibrotic and inflammatory gene induction. Specifically, dichlorofluorescein (DCF) derivatives were quantified in response to radiation. Genes related to oxidative damage (hemeoxygenase-1 [HO-1] and superoxide dismutase [SOD1]), fibrosis (TGFB), and inflammation (cyclooxygenase-2 [COX-2]) were also examined.

Results: Radiation induced a dose and time-dependent effect on ROS synthesis, as well as pro-fibrotic and inflammatory gene expression. Immediately following radiation, DCF derivatives increased in a statistically significant fashion. Increased TGFB, COX-2 and HO-1 expression was observed as early as 24 hours following a single dose of radiation, correlating with increased ROS synthesis suggesting a potential regulatory role of ROS in radiation-induced fibrosis. Conclusion: Our data suggest that fibroblasts of the upper airway respond to radiation by increasing ROS synthesis thereby providing some insight into the underlying pathophysiology of radiation-induced fibrosis. In addition, RT had a direct effect on pro-fibrotic gene expression. In addition, ROS has been shown to activate latent TGFB complexes. This phenomenon warrants further investigation. These data, however, provide preliminary data to consider targeting ROS as a means to prevent/treat radiation-induced fibrosis in patients receiving treatment for malignancy of the head and neck.

S141: THE EPIGASTRIC ADIPOCUTANEOUS FLAP IN RATS AS A MODEL FOR EVALUATION THE EFFECT OF ISCHEMIC PRECONDITIONING A.K.Dacho1, S.Lytenski1, P.Madadi-Sterba2, G.Aust3, A.Dietz4, 1University Hospital Leipzig, Department of Otolaryngology, Head and Neck Surgery, Leipzig, Germany; 2University Hospital Leipzig, Medical and Experimental Center, Leipzig, Germany; 3University Hospital Leipzig, Department of Surgery II, Leipzig, Germany.

Objective: Ischemic preconditioning is a protective endogenous mechanism to reduce ischemia/reperfusion injury and is defined as a brief period of ischemia followed by tissue reperfusion and is believed to increase the ischemic tolerance. The objective of this study was to determine whether acute ischemic preconditioning, which has been reported to be successful for other organs, will also result in an enhancement of survival in flaps, which will be important in reconstructive head and neck tumor surgery, especially in high-risk groups with lots of comorbidities. Methods: Forty-two male Wistar rats weighing 350 g were divided in three equal experimental groups. After induction of anesthesia with ketamine and rompun intraaperitoneally, a vessel clip was inserted into the jugular vein for administration of narcotics throughout the experiment. Oxygen saturation was monitored, and body temperature was maintained constantly between 36.5 C and 37.5 C throughout the experiment using heating pads and lamps. An epigastric adipocutaneous flap (4.5 x 7.5 cm) was raised, based on the superficial epigastric artery and vein. A flap ischemia was induced using a vessel clip with 25 g of compression on both pedicles. The three experimental groups (EG) with 14 animals each were divided after flap raising as follows: EG-Control: suture after 2 hours. EG-Ishemia: Ischemia for 2 hours. EG-Ishemic Preconditioning: Ischemia for 30 minutes, Reperpusion for 30 minutes and Ischemia for 2 hours. Thereafter, the flap was sutured back and placed onto a silicon sheet to prevent neovascularization from the wound bed. Mean flap necrotic area was calculated for each animal using digitized planimetry on postoperative day 5. After completion of the experiment, each animal was euthanized by an overdose of barbiturates. All experiments were approved by the Committee on Animal Rights Protection, and were performed in accordance with the German legislation on protection of animals. Results: There were no differences between the groups regarding age and body weight. Body temperature and heart rate remained stable over the experimental period. Weight gain over the experimental period was 13% for all groups. An adequate social behavior without autocannibalism. The average flap necrosis area was 40.6 ± 11.8 percent in the control group. The average necrosis area was 52.3 ± 14.5 percent in the ischemic group and 48.7 ± 10.4 percent in the ischemic preconditioning group. The group of ischemic animals demonstrated a significantly smaller area of flap necrosis than the control group (p < 0.05).

Conclusion: Our data suggest that ischemic preconditioning increases, as described in other organs, flap survival with a smaller area of necrosis. The epigastric adipocutaneous flap in rats has proved to be an adequate model to evaluate and analyze further therapy approaches based on molecular aspects. Despite the paucity of data available about clinical applications of ischemic preconditioning in reconstructive ENT surgery, the experimental findings are very promising. This might improve the outcome and decrease the complication rate for partial flap loss or fat necrosis, especially in high-risk groups such as patients who smoke or are irradiated like head and neck tumor patients.

S142: FAK-RELATED NON-KINASE (FRNK) BLOCKADE OF FAK INCREASES UVC INDUCED APOTOPSIS IN MURINE SQUAMOUS CELL CARCINOMA CELLS C.M.Biermam1, C.Bien2, A.T. M.MacFall3, M.Dennings4, D.Laning5, 1Maywood, IL; 2Hines VA Hospital, Maywood, IL; 3University of California-Davis, Davis, CA.

Objectives: FAK plays a pivotal role in transmitting signals about cellular processes key to the malignant phenotype, such as cellular invasiveness and cell proliferation. We have previously shown decreased motility and invasion in SCC VII/SF cells transfected with FRNK, the C-terminal, non-catalytic domain of FAK that blocks FAK activity. There is evidence that FAK exerts control over apoptosis in part based on inhibition of caspase 3. In this study, we were interested in how FAK is related to apoptosis activation after exposure to UVC. With this in mind, we hypothesized that blockade of FAK with FRNK would increase susceptibility to UVC induced apoptosis as measured by increased caspase activation and Annexin V labeling. Methods and Procedures: The murine squamous cell carcinoma cell line SCC VII/SF was grown in RPMI 1640 media with 10% serum. Cells were transfected with FRNK and stable transfectants selected. Western blots of total cell lysates of native SCC VII/SF cells and FRNK transfected cells were probed with anti-FAK antibody. To initiate apoptosis, cells were treated with 200 mJ/cm2 of UVC irradiation and used for the subsequent experiments. Transfected cells were compared to sham transfected cells using fluorescent activated cell sorting (FACS) analysis for Annexin V binding and an in vitro fluorescent caspase 3/7 assay. Results: The FRNK transfected cells showed less total FAK on Western blot compared to native SCC VII/SF cells. FRNK transfected cells showed a significantly increased Annexin V positive/7AAD negative staining (p<0.05) 18, 21 and 25 hours after 200 mJ/cm2 of UVC irradiation compared to sham transfected cells. FACS analysis 24 hours after 200 mJ/cm2 UVC irradiation showed a higher percentage of early apoptotic cells (Annexin V positive/7AAD negative) in the FRNK transfected cells compared to sham transfected cells. This increase was still apparent when early and late apoptotic and necrotic cells (all Annexin V positive cells) were counted, although neither of these differences reached statistical significance. Conclusion: Blockade of FAK activity using FRNK leads to increased caspase 3/7 activity up to 25 hours after induction of apoptosis with UVC irradiation. This finding is consistent with the inhibition of caspase activity by FAK noted by others. In addition, early apoptosis after UVC irradiation, as measured by Annexin V positive/7AAD negative staining, is greater in cells in which FAK activity is blocked by FRNK. Total cell death as measured by counting all cells staining positive for Annexin V is also higher in FRNK transfected cells. These data indicate that increased levels of FAK may provide an important selective advantage for squamous cell carcinoma by providing protection from apoptosis-induced death. FAK inhibitors have been recently described. This study lends support to the use of such inhibitors to block FAK activity as another strategy in the effective treatment of squamous cell carcinoma.

S143: DOWNREGULATION OF LET-7 MICRORNA CORRELATES WITH RAS OVEREXPRESSION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA V.F.Wu1, S. Bornstein1, P.E. Andersen1, N.D. Gross1, X.J. Wang1, S.L. Lu1, 1Oregon Health and Science University, Portland, OR.

Objective: Although Ras activation plays an important role in the development of many cancer types, Ras activation was not considered a main contributor to head and neck squamous cell carcinoma (HNSCC) development because of low mutation rates in HNSCC patients in Western populations. However, our recent study shows that Ras overexpression at the pre-translational level occurs frequently in HNSCC, and that Ras activation in our mouse model is sufficient to initiate head and neck tumor formation. Thus, we sought to explore two possible mechanisms of Ras overexpression in HNSCC: 1) through Ras gene amplification and/or 2) through microRNA let-7, which has been shown to downregulate Ras expression. Methods: 9 cases of Kras overexpression, and 9 cases of Hras overexpression in HNSCCs were examined for Ras gene copy numbers and let-7 microRNA expression. SYBR Green qPCR (Applied Biosystems) was used to evaluate
Concomitant chemoradiotherapy (CT/RT) is the standard treatment for locally advanced Head and Neck Squamous Cell Carcinoma (SCCHN). The trial explores the efficacy of induction chemotherapy with Docetaxel/Cisplatin/5Fluorouracil (TPF) administered before concomitant CT/RT and concomitant CT/RT alone.

Patients and Methods: From January 2003 to January 2006, 101 patients with inoperable stage III-IVM0 SCCHN, PS 0-1, were randomized from 18 institutions to receive 2 cycles of Cisplatin 20mg/sqm days 1-4, 5FU 800 mg/sqm 96 hours c.i. weeks 1 and 6 during RT (66-70 Gy) (ARM A: CT/RT alone) or 3 cycles of neoadjuvant TPF followed by the same CT/ARM (ARM B). Ps were stratified according to tumor site, T stage and nodal status. Neck dissection was performed in N2-N3 patients with pathological CR on primary tumor. The sample size was planned to detect a difference in CR (primary endpoint) up to 15% in favor of arm B. The radiological responses were evaluated by an Internal Committee according to RECIST criteria. Based on the efficacy and toxicity data a phase III part of the study was planned. Results: Ps/tumor characteristics were well balanced in the two arms. At the end of CT/RT radiological CR were 21.2% in arm A and 50% in arm B. Toxicities during induction TPF consisted primarily of G3-4 granulocytopenia 52%, febrile neutropenia: 8%. Grade 3-4 toxicities during CT/RT in arm A and B were mucositis (38.7% and 25%), dysphagia (21% and 16%), skin reaction (12.7% and 14.9%), asthenia (5% and 3%), G3 weight loss (2% and 4%). Duration of CT/RT was similar in arm A and B. Conclusions: Three cycles of neoadjuvant TPF are feasible and don’t compromise subsequent concomitant CT/RT with comparable toxicity pattern. A significant difference (26%) in radiological CR evaluated at 6-8 weeks after the end of the treatment was observed in favor of the neoadjuvant TPF arm. The phase III part of the study with the OS a primary end-point is ongoing.

**S144: NEW HIGH THROUGHPUT GENOMIC STRATEGIES FOR THE STUDY OF HEAD AND NECK CANCER**

The human genome project has provided a wealth of information about genome organization as well as a list of all 20,000 human genes. This has facilitated studies to determine which genes are involved in the development of head and neck cancers. However, the greatest impact of the human genome project has been the development of high throughput methodologies that enable researchers to interrogate the entire genome of head and neck cancers. We have been studying base of tongue/tonsillar cancers and oral tongue cancers using these methodologies. We first tested these cancers for the presence of HPV sequences. We found that 45% of base of tongue/tonsillar cancers have HPV sequences while only 1% of oral tongue cancers had HPV sequences. We next began to analyze these cancers using gene expression profiling with the Affymetrix U133 Plus 2 chips to measure gene expression of all expressed genes. We also examined the same samples using array comparative genomic hybridization (aCGH) to characterize copy number variation across the genome. These two high throughput strategies are highly complementary and enabled us to characterize the entire genome of these cancer samples. Key findings were that alterations were distinct between cancers of the oral tongue and base of tongue/tonsil. In addition, we identified differences depending upon whether the individual who developed a specific cancer was a smoker or not. We are currently validating the expression of key genes that are altered in these cancers using real-time RT-PCR. While these high throughput strategies are powerful there is new developing chemotherapeutics. As these new agents are developed we will be able to exploit the expression data to identify new therapeutic targets. In addition, this information can also be used to inform better clinical decisions.

**S146: TREATING ORAL MUCOSITIS WITH RESORBABLE LAMINATED REPAIR MEMBRANE FOR LOCAL DELIVERY OF KERATINOCTYE GROWTH FACTOR**

The objective of this study is to develop a biodegradable synthetic local matrix system to deliver Keratinocyte Growth Factor (KGF) to improve epithelial migration and proliferation (mucosal repair) in the treatment of oral mucositis. Up to 90% of patients treated with concurrent chemoradiation therapy for head and neck malignancies suffer debilitating oral mucositis. Patient outcomes can be negatively impacted when their dosing and treatment schedules or nutritional status are altered because of mucositis. The systemic administration of keratinocyte growth factor (KGF) ameliorates the severity of these treatment-related mucositis. Unfortunately, systemic treatment of oral mucositis with KGF is limited by dose-related dermatologic toxicities. This issue could be overcome if one could selectively deliver KGF to the area of injury. Toward this end, we have developed a prototype synthetic resorbable biomaterial that incorporates biologically active KGF within the material. As the biodegradable material erodes, KGF is released in a choreographed, precise, and sustained manner to the injured oral mucosal epithelium, improving cell attachment and proliferation - key components of epithelial repair and mucosal integrity. Methods: Oral keratinocytes (porcine model) were isolated and cultured simulating primary oral mucosal injury (desquamation). After injury these cells attached, migrated, and proliferated on synthetic membranes formulated with endogenous KGF. All cultures were analyzed for cell morphology, viability, and adhesion. Results: When exogenous KGF or KGF from the
Over the last 2 decades, survival from laryngeal cancer has increased. Between February 1988 and December 2005, 619 patients (578 males, 41 females; age range, 29-88 years, mean, 62) were treated at a single academic institution for Tis-T3 glottic cancer with CO2 laser. 597 (96%) previously untreated patients were classified as follows: 72 pTis, 312 pT1a, 92 pT1b, 17 pT1c, 131 pT2, 40 pT3a, 60 pT3b, and 13 pT3c. Five-year survival rates were 85% for stage I, 77% for stage II, 51% for stage III, and 35% for stage IV disease. Survival for patients with stage III disease was similar for patients treated operationally or nonoperatively (p=0.4); however, patients with stage III disease treated nonoperatively had worse survival with radiation alone (XT) compared to chemotherapy (CR) (p<0.0001). Patients with stage IV disease had significantly better survival with surgery (48%) than CR (25%) or XT alone (15%) (p<0.0001). Analysis by primary tumor or stage of cancer showed that survival for T1-T3 disease was independent of treatment modality (p=0.2); in T4 patients, operative treatment was associated with significantly better survival (55%) than CR (21%) or XT (0%) (p<0.0001). When patients were divided into those who were past medical history positive and those who were negative, no significant difference was noted between the groups in terms of survival. The impact on determine survival, local control with laser alone, and organ preservation rates of different variables (pt category, involvement of the anterior comissure, ventricle, vocal muscle, supra- and/or subcommisural areas, and subglottis, surgical margins, previous RT, complementary RT, and endoscopic resection for positive margins) was evaluated by univariate analysis with the log-rank test. Results: Overall and determine survival, local control with laser alone and organ preservation rates were 86.8%, 98.9%, 93.5%, and 97.1%, respectively. Among 108 recurrences (17%), 2 were salvaged by RT, 11 by chemo-R, 51 by endoscopic resection, 20 by endoscopic resection followed by RT, 9 by conservative open-neck surgery, and 25 by total laryngectomy with or without RT. Univariate analysis showed a statistically significant impact of endoscopic resection for positive margins on determine survival, local control with laser alone, and organ preservation rates (p=0.02, p=0.03, and p=0.03, respectively) and of PT category on local control with laser alone and organ preservation rates (p=0.0001 for untreated tumors and p=0.04 for recurrent tumors after RT). Conclusions: This series enhances the overall good oncologic outcome of endoscopic treatment in Tis, T1, and T2 glottic tumors. However, one of the most important variables affecting local control and organ preservation rates has been demonstrated to be the need for re-resection due to positive margins. This highlights the importance of an accurate tumor staging and appropriate margin of resection at the time of the first treatment.
Functional and anatomic imaging has improved our ability to evaluate patients who received intensity modulated postoperative radiation therapy (IMRT) at WUMC. Methods and Materials: From June, 1997 to July, 2006, 78 patients underwent TLM for squamous cell carcinoma of the head and neck and received IMPORT at WUMC. Tumor subsites included the oropharynx (n=57), oral cavity (n=8), larynx (n=8), and hypopharynx (n=5). Ultimate surgical margins were negative in every case. Indications for radiation included close surgical margins (<5 mm), more than one positive lymph node metastasis, or extracapsular extension in any lymph node. The 5th edition of AJCC TNM staging was used to assess the stage of tumor. Results: Stage III/IV disease accounted for 96% of patients with 23% having T3-T4a disease. There were 68 males and 10 females, and the median age was 58 years. Chemotherapy was delivered concurrently with radiation in 36% of patients. At a median follow up time of 34 months (range 4-105), the local control rate was 100% and the regional control rate was 96%. Five patients developed second primary tumors, and 11% (8/75) developed distant metastasis. Quality of life was assessed with the functional outcome swallowing scale (FOSS) and was available for all patients. The mean FOSS score was 0.83 (range 0-5). Both the median and mode of the FOSS scores were zero. Conclusions: TLM and IMPORT represent less invasive forms of surgical resection and radiation therapy, respectively. In our experience, the combination of these minimally invasive approaches results in excellent local-regional control in patients with locally advanced squamous cell carcinoma of the head and neck. Functional status based on the FOSS scale is encouraging.

S151: PREDICTIVE FACTORS FOR OCCULT METASTASES IN SENTINEL LYMPH NODES OF EARLY ORAL SQUAMOUS CELL CARCINOMAS
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Objective: Sentinel node biopsy (SNB) for clinically N0 early squamous cell carcinomas of the oral cavity and oropharynx has been validated by numerous studies, and gained worldwide popularity. Many centers have introduced the concept of SNB in their daily routine. Between 30 and 40% of sentinel nodes have been shown to contain microscopic tumor deposits not detected by pretherapeutic imaging. In the past, several clinical and morphological features of the primary tumors have been claimed to be predictive for occult lymph node metastasis in elective neck dissections. The aim of this study was to assess whether these clinical or morphological factors were still significantly predictive in the context of SNB. Methods: All patients undergoing SNB for an early (T1/2) oral squamous cell carcinoma from the years 2000 to 2007 were prospectively included. The sentinel nodes were worked up by step serial sectioning at intervals of 150 microns, and staining with H&E and cytokeratin. The primary tumors were reviewed for following morphological features: grade of differentiation, tumor depth, tumor thickness, perineural invasion, lymphatic invasion, vascular invasion, lymphoplasmacytic infiltration, and mode of invasion (cohesive vs. dissociate). In addition, following clinical parameters were assessed: age, gender, primary tumor site, and cTNM category. Statistical analysis was performed using a univariate logistic regression model. P-values less than 0.05 were considered as significant. Results: The total number of 78 patients (52 males, 26 females) were included in the study. Statistical analysis revealed significance to predict occult metastasis in the sentinel lymph nodes for the grade of differentiation (p=0.001), lymphatic invasion (p<0.001) and mode of invasion (p=0.001). None of the other factors reached statistical significance: age (p=0.974), gender (p=0.739), site of the primary tumor (p=0.894), cTNM (p=0.865), tumor depth (p=0.363), tumor thickness (p=0.455), perineural invasion (p=0.714), vascular invasion (p=0.270), lymphoplasmacytic infiltration (p=0.515). The mean tumor depth was 6.5mm (range: 0.7-15.1mm), and the mean tumor thickness 7.2mm (range: 0.7-15.1mm). Using the cut-off value of tumor depth the negative predictive value achieved only 66%. Conclusions: The most commonly used predictive factors for occult lymph node metastasis in the clinical setting of elective neck dissection are tumor depth and tumor thickness. Both of these factors failed to achieve statistical significance in the context of SNB. The cut-off value of tumor depth of less than 5mm correctly predicted a histologically negative neck in only two thirds of the patients, therefore, this paradigm should be abandoned. Patients with cN0 early squamous cell carcinoma of the oral cavity should be offered SNB regardless of their tumor depth and thickness. Poorly differen- tiated carcinomas, carcinomas with lymphangiosis, and carcinomas with a dissolute mode of invasion show a high probability of positive SNB, and will need elective neck dissection in a high proportion of cases.

S152: SENTINEL LYMPH NODE BIOPSY FOR CLINICALLY NODE-NEGATIVE SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY
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Objectives: This prospective study was performed to assess the technical feasibility of sentinel lymph node (SLN) biopsy and validate the role of SLN biopsy against elective neck dissection in clinically node-negative early oral cancer. Methods: Between 2002 and 2007, a total of 33 patients were enrolled (22 males, 11 females) in the present study. Eligible patients had clinical stage T1/2 and N0 squamous cell carcinoma of the oral cavity. After the peritumoral injection of 99m Tc filtered tin colloid, preoperative lymphoscintigraphy and intraoperative use of a hand-held gamma probe were used for lymphatic mapping and sentinel lymph node detection. Neck dissections were performed in combination with SLN biopsy. Mean duration of follow-up was 25.2 mo. Results: Both lymphoscintigraphy and gamma probe showed a high SLN detection rate of 96.9% and 100%. A total of 78 SLNs were localized in 33 patients with 11 positive SLNs in 9 patients. Negative predictive value of intraoperative frozen section analysis showed 98.5%, and that of SLN biopsy permanent pathological analysis with immunohistochemical analysis was 100%. Additional non-sentinel positive lymph nodes in neck dissection specimens were found in 2 out of 9 patients with positive SLN but in none out of 24 patients with negative SLN, which means negative predictive value of negative SLN for the remaining neck to be 100%. Regional failures were occurred in 3 patients (9%), all of them had positive SLN. Conclusion: SLN biopsy using lymphoscintigraphy and gamma probe was technically feasible. Application of SLN biopsy in clinically-node negative oral cancer appears to predict the occult metastasis rate accurately with a negative predictive value of 100% in the present study.

S153: GUIDELINES FOR NECK DISSECTION AFTER CONCOMITANT CHEMORADIATION IN PATIENTS WITH OROPHARYNGEAL SQUAMOUS CELL CARCINOMA
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Objective: Function and anatomic imaging has improved our ability to assess treatment response. Concurrent chemoradiation for patients with oropharyngeal squamous cell carcinoma has improved response in the neck. These advances have resulted in re-evaluation of the need for post treatment planned neck dissection in patients who present with neck adenopathy greater than 3 cm. To address this issue we compared a group of patients with oropharyngeal cancer who underwent planned neck dissection versus patients who underwent an elective neck dissection only if residual disease was diagnosed with functional or anatomic imaging. We aimed to determine if planned neck dissection improved regional control, distant metastasis pattern, disease specific survival and overall survival in patients presenting with neck metastasis greater than 3 cm from oropharyngeal cancer. Methods: A quasi-experimental study comparing patients who underwent planned neck dissection after chemoradiation versus patients who underwent chemoradiation with elective neck dissection only for patients indicated by anatomic or functional imaging was performed. Patients were enrolled and consented to the SPORE program as they presented to the University of Michigan, Department of Otolaryngology from 2003-2006. Eligibility criteria were previously untreated squamous cell carcinoma, neck metastasis ?3 cm, primary treatment with concurrent chemoradiation and minimum 1 year of follow-up.74 patients were evaluated. Mean age, 56.6; range (35-82); M:F, 67:7. Clinical and treatment information was obtained from the SPORE database and the medical record. 31 patients were treated with chemoradiation and planned dissection while 43 patients were treated with chemoradiation and elective dissection. Patient
outcomes were assessed for site of recurrence, number of metastatic sites, regional control, disease specific and overall survival and HPV status. Treatment variables assessed were imaging modality, imaging findings and neck dissection type. A cross-section of surviving patients were evaluated using the Neck Dissection Impairment Index (NDII) to assess the impact of neck dissection on shoulder function after chemoradiation. Results: Patients who were committed to planned neck dissection were not shown to have significantly reduced rates of regional or distant metastasis, local recurrence, or reduction in overall or disease specific survival. Six patients from the elective group went on to require dissection (13.9%). One of these patients later developed primary recurrence, and none developed local or regional metastases. The proportion of patients with negative neck dissection between the two groups was comparable. Among patients who developed distant metastases, those who had undergone either planned or elective neck dissection showed an average of .75 fewer metastatic sites (p=.09) and had significantly reduced mortality from their disease (p=.01).

Conclusions: Planned neck dissection does not confer advantages in survival or recurrence rates in patients treated with chemoradiation for oropharyngeal squamous cell carcinoma when compared with elective neck dissection indicated by only post treatment evaluation with anatomic and functional imaging appears effective in identifying regional disease that requires aggressive treatment. Patients who have a complete response regionally to concomitant chemoradiation as assessed by anatomic CT imaging, and functional PET imaging do not require neck dissection.

CLINICAL: THYROID III

S154: PROPHYLACTIC CENTRAL LYMPH NODE DISSECTION IN PAPILLARY THYROID CANCER Costa 1, A.Ywata2, N.Tradati3, B.Gibelli3, E.Grosso3, G.Giugliano3, A.Ramirez4, L.Calabrese4, L.Kowalski2, F.Chiessa3, 1Istituto Europeo di Oncologia (IEO), Università degli Studi, Milan, Italy; 2Hospital do Câncer A.C. Camargo, Sao Paulo, Brazil; 3Istituto Europeo di Oncologia (IEO), Milan, Italy; 4University Hospital, Neiva, Colombia

Objective: Prophylactic central neck dissection in cN0 papillary thyroid cancer (PTC) is controversial. The aim of this study was to assess the safety and benefit of elective central lymph node dissection (CLND) combined with total thyroidectomy.

Design: Single Institution retrospective cohort study. Setting: Istituto Europeo di Oncologia (IEO), Milano, Italy. Patients: From 1994 to 2002, 129 consecutive patients entered the study. All of them underwent the same preoperative Tg assay (group A1 had a preoperative diagnosis of PTC and 74 (group B) not (follicular neoplasia, incidental microcarcinoma in goiter). Intervention: Group A underwent thyroidectomy and ipsilateral CLND, group B thyroidectomy alone. Demographic, clinical and anatomo-pathological features, including pre- and post-operative levels of thyroglobulin (TG), were analyzed. pT3, pT4, pT1-4 (m) pN1 patients underwent post-ablative thyrotoxic therapy. Nodal recurrence occurred in 16.6% in group A and 6.6% in group B. Only 8.3% of Group A patients without nodal metastasis developed a relapse, hence the risk was higher among the patients with nodal metastasis (25%). Among Group B 75% of cases recurred in the VI level, and among Group A the same percentage relapsed in the lateral neck. Survival rate was the same in the two groups: all the patients are alive, two with a persistent disease.

Results: The patients of the two groups were similar for gender and age at diagnosis. Group A had a median follow up of 60 months and group B of 57; 20 patients (15.5%) were lost to follow-up. In group A 28 patients (50.1%) were pN1 and the tumors were greater in size pT3-T4a=43.6%), than in group B (pT3=14.8%). The two groups were equivalent for histological variants with adverse prognosis (follicular, tall cell, Hurtle, desmoplastic, sclerosing) and multifocality. According to the pT distribution, a higher extracapsular invasion rate was observed in group A (65.5%) than in group B (27%). A lower risk of nodal metastasis was related with thyroiditis (N0=37% and N1=14%) in group A, but it was not associated with histological variants or multifocality. Nodal metastasis were related with cancer stage: 64.3% pT3-T4a in pN1 vs 22.2% in pN0. Percentage of non-producing tumors malignancies was also significantly post-ablative. Pre-ablative serum TG was equivalent in group A (1.55 ng / ml) and group B (1.02 ng / ml). Similar complication rate was observed in the two groups.

Conclusions: CLND did not increase the risks of thyroidectomy and did not modify the post-ablative TG-levels. Lymph nodes metastases were more frequent in advanced tumours but less frequent in presence of thyroiditis. Central neck nodal metastases were predictive of a higher incidence of regional recurrence and necessity for further treatment but did not influence 5-year prognosis. Further improvement of both tumoral and nodal diagnosis should help in planning adequate surgery.

S155: CENTRAL COMPARTMENT LYMPH NODE METASTASIS IN WELL-DIFFERENTIATED THYROID CARCINOMA D.I.Kulier1, A.B.Crummey1, W.I.Kuhel1, 1Weill Cornell Medical College, New York, NY

Background: Lymph node metastasis of well-differentiated thyroid carcinoma is a common finding. Nodal metastases most frequently occur in the central compartment, and may be present in 33-64% of all well-differentiated thyroid cancers. Certain factors have been associated with greater risk for lymph node involvement, including older age, larger tumors, and tumor invasion. It has been proposed that central compartment node dissection is optimal in order to avoid the morbidity associated with multiple surgical procedures; however, there has been little consensus among head and neck surgeons in this regard. This study describes the group of patients at our institution found to have central compartment nodal metastases during surgical resection of papillary thyroid cancer; in particular, we focus on the correlations between patient age and primary tumor size on rates of central compartment lymph node metastasis.

Methods: This study is a retrospective chart analysis of 107 patients (mean age, 48 years; range, 11 to 80 years) treated with papillary thyroid carcinoma and operated on by one surgeon, W.K. Surgeries took place between January 1999 and November 2006. Patients received either total or hemithyroidectomy, accompanied by lymph node dissection when determined necessary. Results: Of 107 patients, central compartment nodal dissections were performed in 79 patients (73.8%). Thirty-four of these patients were found to have metastases in the central compartment (43%). An average of 8.8 total lymph nodes were removed during central compartment dissection (range: 1 to 37). The average number of positive nodes was 4.53 (range: 1 to 16). Thirty-four of the 79 patients (43%) receiving central compartment dissection were older than 45 years of age, while 45 patients (57%) were under 45 years of age. Positive central compartment node metastases were found in approximately equal rates between older and younger patients (41.2% and 44.4%, respectively). The primary tumor was a microcarcinoma (1 cm or less) in 29 patients (36.7%) and greater than 1 cm in 50 patients (63.3%). Positive central compartment node metastases were detected in 34.5% of the patients with microcarcinomas, compared to 48% of the patients with tumors greater than 1 cm. When performing an analysis of the combined factors of age and primary tumor size, patients who were under the age of 45 years with tumors larger than 1 cm had the highest overall incidence of positive central compartment metastasis (51.5%), while patients of the same age group with microcarcinomas had the lowest incidence (25%). In patients over 45 years of age, the rates of central compartment metastases were equal for both tumor size groups (41.2%).

Conclusion: Central compartment nodal metastases are common in well-differentiated thyroid cancer. Nodal metastases were more frequent in advanced tumours but less frequent in presence of thyroiditis. Central neck nodal metastases were predictive of a higher incidence of regional recurrence and necessity for further treatment but did not influence 5-year prognosis. Further improvement of both tumoral and nodal diagnosis should help in planning adequate surgery.

S156: EXTENT OF PROPHYLACTIC LYMPH NODE DISSECTION IN THE CENTRAL NECK AREA IN PATIENTS WITH PAPILLARY THYROID CARCINOMA H.Jeong1, Y.Son1, C.Baek1, M.Chung1, Y.So1, J.Jang1, K.Park1, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Objectives: To compare the comprehensive central node dissection (CCND; including bilateral paratracheal, pretracheal, prelaryngeal lymph nodes) with the limited central node dissection (LCND; saving contralateral paratracheal lymph nodes) for postoperative complications and disease recurrence rate in ultrasonographically node-negative papillary thyroid carcinomas. Methods: From 2003 to 2005, 114 consecutive patients, diagnosed as sonographically node-negative thyroid papillary carcinomas, were included in this study. Among them the LCND was performed in 56 patients and CCND in 58 patients, in combination with total thyroidectomy. We compared the complications and the recurrence rate between these two groups with a mean follow-up duration of 2 years. Results: Transient hypocalcemia was more frequent in the CCND group than in the LCND group (48.3% vs. 26.8%, P=0.02, OR=2.55). An immediate post-operative reduction of parathyroid hormone (PTH) was more evident in the LCND group (48.3% vs. 26.8%, P=0.02, OR=2.55). An immediate post-operative reduction of parathyroid hormone (PTH) was more evident in the LCND group (48.3% vs. 26.8%, P=0.02, OR=2.55). 148 www.ahns.info
fer in between the two groups. The postoperative PTH values reached to a similar level (12.4 vs. 11.8 pg/ml) at around 6 months after the surgery. Four (7.1%) and five recurrences (8.6%) were found in the LCND and CCND group respectively, implying a similar oncological safety when compared at 2-year follow-up. Conclusion: The LCND and total thyroidectomy could be an alternative treatment option for node-negative papillary thyroid carcinomas, because LCND had fewer short-term hypocalcemia and similar oncological outcomes during the 2-year follow-up. Further study enrolling a large number of patients with long-term follow-up is needed.

S157: ARE THERE COLLOID NODULES THAT REQUIRE NO PUNCTURE? E Horvath 1, S Majlis 1, J Iliausq 1, E Soto 1, J Niedmann 1, A Castro 1, A Madrid 1, H Rojas 1, R Rossi F 1, F Capdeville 1, 1 Clinica Alemana, Santiago, Chile

Introduction: We found nodules by sonography in approximately 40% of the general population. The most frequent nodules are the benign colloid ones. Their indiscriminate puncture means a significant raise in cost for the health services, and it also generates additional stress in patients.

Objectives: The objective of this study was to classify the US punctured thyroid nodules, to describe the echographic aspects of colloid nodules and to define the colloid patterns with low malignancy association in order to reduce the unnecessary diagnostic punctures. Database registering (FileMakerPro®) of 1188 consecutive thyroid nodules, studied histologically by puncture (19G needle, blood clot technique) between February 2002 and February 2007. They were classified into five echographic patterns (Type 1, 2, 3, characteristic of colloid nodules, Neoplastic pattern and Malignant pattern). Each pattern is described, as well as its association with malignant lesions. Results: 619 colloid nodules have been diagnosed by fine needle aspiration (FNA) in 541 patients (462 women and 79 men, from 16 to 82 years of age, mean age=52.3), representing 52% of the series. They have been classified in 5 groups according to their echographic aspect: Type 1= (anechogenic with hyperechogenic spots) (9=1.5%), Type 2= (vascularized “grid”) (10=1.6%), Type 3= (mixed nodule with isoechogenic solid component, non encapsulated, vascularized) (397=64.1%), Neoplastic Pattern= (solid or mixed nodule iso., hypoechogenic, encapsulated, vascularized) (169=27.3%), and Malignant Pattern= (hypoechogenic, non encapsulated with or without calcifications with penetrating vessels) (34=5.5%). In the total series, the incidence of cancers was 0%, 0% and 1.42% in the patterns Type 1, 2 and 3 respectively, 10.25% in the Neoplastic Pattern and 64.94% in the Malignant Pattern. Conclusions: Colloid nodules may mimic all type of nodules on echography. However 67.2% of them have a characteristic echographic pattern (pattern Type 1 to 3), low association with cancer (<2%). When they are recognized as such, it would be recommendable to indicate echographic follow-up, thus significantly lowering the rate of unnecessary diagnostic punctures.

S158: QUALITY OF LIFE IN PATIENTS WITH WELL-DIFFERENTIATED THYROID CARCINOMA J.P. Almeida 1, L.N. Nishimoto 1, J.G. Vartanian 1, E.N. Pimenta 1, I.P. Kowalski 1, Hospital A. C. Camargo, São Paulo, Brazil

Objectives: Patients with well-differentiated thyroid carcinomas usually present a good prognosis with overall survival rates over 90%. Traditionally, the evolution of cancer patients has been evaluated by the survival years. Recently, it has been acknowledged that the diagnosis and treatment of cancer have also a strong impact on the quality of life of these patients. This study aims to evaluate the quality of life in thyroid cancer patients and evaluate if different modalities of treatment can interfere in the quality of life.

Methods: 162 patients submitted to thyroidectomy from 1997 to 2006 were evaluated through the Washington University - Quality of Life Questionnaire. Results: the mean overall score was 91.1 and the median was 93.7. From 162 evaluated patients, 101 had been submitted to radioactive iodine therapy (RIT) and 61 were not, and there was no significant difference between the groups. Although the median scores in the group of patients that received less than 150mCi and that received more than 150mCi are over 75 (95.17 and 88.92, respectively) there was not significant difference between these values (p = 0.002). 16 patients presented scored less than 75 (with moderate/severe alterations in the quality of life). From these 16 patients, 12 had been submitted to RIT and 4 were not (p = 0.20). In this subgroup, 3 patients presented severe pain, one reported significant alteration of the appearance limiting his activities, 7 reported to be tired diminishing their activities and one reported severe limitation to recreational. On the functional domains, swallowing, chewing, speaking, taste, salivation and shoulder were also evaluated. Ten patients reported to have their shoulders weak and painful, 4 patients reported stressed taste disturbance and one patient reported xerostomia. In the group of patients with RIT, doses over 150mCi showed an association with chewing and swallowing scores less than 75 (p = 0.002 and p = 0.039, respectively). The other domains did not show significant alterations.

Results: These results show that the treatment of well-differentiated thyroid carcinoma impacts on the quality of life of these patients when they are submitted to adjuvant RIT with doses higher than 150mCi, because the interference with chewing and swallowing functions.

S159: THYROID CANCER IN HYPERPARATHYROID PATIENTS UNDERGOING RADIOGUIDED PARATHYROIDECTOMY S. Saba 1, E. Walsh 1, V. Rao 1, M. Ghanem 1, M. Rajji 1, D. Wease 1, J. Hammond 1, M. Bakleh 1, J. Nelson 1, N. Tomycz 1, M. Lecaryn Regional Medical Center, Flint, MI; 2 Synergy Medical Education Alliance, Saginaw, MI; 3 Genesys Regional Medical Center, Grand Blanc, MI

Objective: Minimally invasive radioguided parathyroidectomy (MIRP) became a common procedure after the advent of Tc-99m sestamibi parathyroid scans (SPS), and is indicated in +ve SPS patients suggesting a single parathyroid adenoma. Though the procedure has the advantages of short recovery times and fewer complications than bilateral surgery, it fails to identify cancerous parathyroid tissue, which occurs in 40-50% of hyperparathyroid patients. To further examine this issue, we undertook a prospective study to determine the rates of thyroid pathology in patients undergoing radioguided parathyroidectomy.

Methods: Patients with a +ve SPS and -ve TUS underwent MIRP. Patients with a +ve TUS underwent fine needle aspiration and bilateral neck exploration with radioguided parathyroidectomy regardless of SPS results. Total or partial thyroidectomy was performed as indicated. Results: Our study included 252 consecutive hyperparathyroid patients (M:F=68:184, and mean age=62.2). SPS was positive in 186 (74%) patients, negative in 58 (23%), and equivocal in 7 (3%). One patient was unable to tolerate SPS. The following parathyroidopathies were identified: adenoma in 190 (75.4%), hyperplasia in 42 (16.7%), double adenoma in 9 (3.6%), cyst in 1 (0.4%), and parathyroid carcinomas in 2 (1%) of the patients respectively. Additionally, no parathyroid pathology was identified in 9 (3.6%) of the patients. Thyroid pathology requiring surgical resection was found in 135 (54%) patients, and included goiter in 85 (34%), Hashimoto’s in 33 (13%), papillary carcinomas in 19 (8%), and follicular adenoma in 5 (2%) patients respectively. Five surgical resections were found to be benign thyroid tissue, these resections were performed for infra thyroidal parathyroid adenomas. Among the 19 patients found to have papillary carcinomas, TUS was positive in 16 (89%) and negative in 2 (11%) patients. All 19 of these patients were asymptomatic papillary carcinomas with their initial presentation. Metastatic disease to lymph nodes was present in 2 (11%) patients at the time of surgery.

Conclusion: Preoperative TUS allowed us to identify operable thyroid pathology in 54% of our patients and helped to identify asymptomatic papillary carcinomas which would have gone undetected had these patients undergone MIRP only. Since the prevalence of thyroid pathology is high in patients with hyperparathyroidism, preoperative TUS and fine needle aspiration may help stratify patients who are ideal candidates for MIRP from those that should undergo bilateral radioguided parathyroidectomy along with thyroidectomy.

S160: THE RELATIONSHIP BETWEEN THYROID NODULE SIZE AND THE RISK OF MALIGNANCY N. A. Pagadar 1, L. J. Freeman 1

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Introduction: The incidence of thyroid cancer has increased substantially over the past two decades, yet malignancy remains an uncommon finding in thyroid nodules. In the absence of a perfect clinical diagnostic test for malignancy, the goal of the evaluation is to determine which patients have high enough risk for cancer that thyroidectomy would be advisable. Known risk factors for cancer include patient factors (age over 60 years, male gender), clinical findings (vocal cord immobility, cervical lymphadenopathy, fine needle aspiration biopsy), and sonographic findings (microcalcification). Large nodule size has been identified as a risk factor, but is not universally accepted as such. We sought to determine whether clinicians should be more suspicious of large nodules than small nodules.

Materials & Methods: After receiving Research Ethics Board approval, we reviewed the charts of 500 consecutive patients who underwent thyroidectomy by the three surgeons in our department. We included only patients with solitary
In this retrospective review, large thyroid nodules were identified. The cytohistology had the following distribution: 702 (64%) benign, 158 (14%) malignant, and 237 (22%) FL. The TIRADS classification (BI-RADS System) of the American College of Radiology classifies the mamographic appearance of breast masses and breast ultrasound findings, in order of increasing risk for cancer, with criteria for recommending further management including FNA. We propose an analogous scoring and reporting system to classify the nodules: 1º colloid type (CT) 1 (anechogenic with a hyperechogenic spot), 2º colloid type (CT) 2 (grid), 3º colloid type (CT) 3 (small hypoechogenic spot), 4º pseudonodule, 5º hypoechogenic pattern, 6º suspicious neoplasm (encapsulated nodule), 7º malignant (MP A, B, C, D). The TIRADS classification establishes a common language and program system for radiologists and for clinicians that can guide a cost-effective management of thyroid nodules.

**T160: THYROID CANCER**

**M.Lobo 1,** A.S.Garden 1, W.H. Morrison 1, K.K. Ang 1, D.Rosenthal 1, C. Chao 1, D.B. Evans 1, G. Clayman 1, S. Sherman 1, D.L. Schwartz 1, 1UT M.D. Anderson Cancer Center, Houston, TX

**Purpose:** The thyroid is a technically challenging location for delivery of high-dose radiation due to the proximity of dose-limiting anatomy. Intensity-modulated radiation treatment (IMRT) permits conformal dose coverage and provides the promise of improved therapeutic index. We retrospectively reviewed our institutional experience with the use of IMRT for differentiated thyroid cancer.

**Methods:** Seventy-seven consecutive patients were treated in our department with IMRT between 8/2000 and 12/2005. Sixty patients had differentiated histology (53 papillary and 7 follicular) and were analyzed further. Median age was 57 years (range: 21-83, with 52 patients > 45 years old) and male/female ratio was 3:2. Nineteen (22%) patients had high-risk histology (5 tall cell, 4 Hurthle cell, 3 poorly differentiated, and 1 clear cell) and 32 (38%) had recurrent disease. T and N stage was cataloged from index presentation and M stage status was cataloged from time of start of IMRT. There were 1 T1, 4 T2, 48 T4, and 1 T5 stage cases. Forty (52%) patients had N1 disease and 15 (25%) patients were M1. AJCC stage distribution was stage I, 1 stage III, 5 stage IVa-c, and non-accessible in 2 cases. All underwent primary or salvage surgery prior to radiation. Extensive extraglandular disease extension was seen in 52 (87%) cases; there were positive surgical margins in 19 cases or gross residual disease in 9 cases. A median of 3 positive nodes (range: 0-25) were removed from N1 patients, whereas these patients had extracapsular extension. Radioactive iodine was given to 48 (80%) patients, while chemotherapy was given to 8 (13%). Median total IMRT dose was 60 Gy [range: 54-66 Gy] in 30 fractions [range: 27-33]. Median follow-up was 32.5 months (range: 5-85) for all patients and 35 months for surviving patients (range: 6-85).

**Results:** At last follow-up, 50 (83%) patients were alive, and 48 (80%) patients achieved locoregional control. All 12 locoregional failures occurred within 26 months of IMRT. Kaplan-Meier estimates of locoregional relapse-free survival (LRFs), disease specific survival, and overall survival (OS) at 5 years were 78%, 82%, and 81%, respectively. Eleven of 45 MO patients (24%) developed distant failures following IMRT. No clinical or disease factor predicted for LRFs or Cox proportional hazards analysis; 8/9 patients with gross residual disease were controlled locoregionally with a median follow-up of 25 months. Distant disease at the time of IMRT was of borderline significance for predicting OS, with 62% estimated 5 year OS for M1 patients vs. 87% for M0 patients (p = 0.052). Three (5%) patients reported symptomatic late post-IMRT morbidity, including 2 cases of xerostomia/dysphagia (one requiring PEG-tube placement) and one case of long-term tracheostomy placement.

**Conclusions:** IMRT provides durable locoregional disease control with relatively limited long-term morbidity. Patients with locally advanced differentiated thyroid cancer frequently enjoy long-term survival, making optimal locoregional management an imperative. IMRT for thyroid disease merits further study to determine ideal planning target volume design and dosing.

**EPIDEMIOLOGY**

**S163: INTESTINAL TYPE ADENOCARCINOMA OF THE ETHMID SINUS: AN OCCUPATIONAL DISEASE**

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**Objective:** To assess the relationship between ethmoid intestinal type adenocarcinoma (ITAC) and exposition to wood or leather dusts. **Methods:** The medical records of 706 consecutive patients surgically treated for malignant tumors of the paranasal sinuses from January 1987 and September 2007 were reviewed. We decided to start the beginning of our data analysis in 1987 as from then on all patients with paranasal sinus malignant tumors were specifically asked about their occupational history. Tumor site was classified as maxillary or ethmoid sinus. Ethmoid tumors included lesions originating in the middle and/or superior turbinate, or in the ethmoid patients (44.8%), whereas squamous cell carcinoma (SCC) was the most frequent in maxillary sinus patients (34.9%). We found an exposi-
tion to organic dusts in 181/402 (45.0%) patients with ethmoid tumor and in 4/304 (1.3%) patients with maxillary tumor. For these later, 3 patients with squamous cell carcinoma have been exposed to wood, leather and asbestos (one each), and 1 patient with undifferentiated carcinoma resulted exposed to wood dust. Regarding ITACs, 166/180 (92.2%) patients have been exposed to organic dusts, mainly wood and leather (56.7% and 35.6%, respectively). There was exposition to textile, asbestos and rise dusts in one patient each. Most ITACs patients have been exposed to organic dusts for a minimum of 25 years to a maximum of 55 years. A group of 17 patients had experienced a very early and limited exposure (from 4 to 18 years), followed by a long interval between the end of exposure and the onset of the disease (from 23 to 46 years). Conclusions: Many authors have already highlighted the increased odds ratios for the development of sinonasal ITACs in those workers exposed to wood or leather dusts. At our knowledge, our series of ITACs is the largest in the world. From our study we can confirm that most patients with ethmoid ITAC have had a previous exposure to wood or leather dusts. This percentage is so high that we can consider this malignancy as an indisputable occupational disease. In the light of these results, all available technology should be employed to remove wood and leather dust from work places and to prevent workers from inhaling these oncogenic agents. On the other hand, we was unable to establish any significant relationship between organic dusts exposure and ethmoid malignancies other than ITAC, or tumors originating from other parasinal sinuses.

S164: SIXTY YEAR CANCER CENTER EXPERIENCE WITH OROPHARYNGEAL CARCINOMA: YOUNGER PATIENTS, LESS SMOKING, & IMPROVED SURVIVAL
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Objective: To examine the trends over time in demographics, clinical presentation, and exposure history of patients with newly-diagnosed oropharyngeal carcinoma at a tertiary cancer center. Methods: Retrospective chart review using the institutional tumor registry, of all patients presenting with newly-diagnosed, untreated oropharyngeal squamous cell carcinoma from 1945 to 2005 at a tertiary cancer center. We evaluated age, sex, ethnicity, histology, clinical stage, primary site, tobacco exposure, alcohol exposure, and overall survival. Results: Since 1945, 4140 patients have presented with oropharyngeal squamous cell carcinoma. There is a significant trend for younger age of presentation (P < 0.001) for patients with oropharyngeal carcinoma. The mean age has dropped from 62 in the 1950s (2% of patients under 40) to 56 in the most recent decade (6% of patients were under 40). In addition, there appears to be decreasing tobacco exposure in the most recent years (P < 0.001) and higher incidence of nodal metastasis (P < 0.001). Overall crude 5-year survival has improved from 30% in the 1950’s to 60% in the most recent decade (P < 0.001). Other trends in demographics, clinic characteristics, and survival may be described and presented. Conclusions: The sixty year experience of oropharyngeal carcinoma revealed a younger age of presentation, with less tobacco exposure, and overall improved survival. These trends may well likely reflect a rising prevalence of human papillomavirus type 16 and improved multimorbidity care.

S166: SOCIOECONOMIC STATUS AS A PREDICTOR OF SURVIVAL IN HEAD AND NECK CANCER PATIENTS
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Objective: The purpose of this study is to identify if race/ethnicity and socioeconomic status are associated with disparities in all cause survival among newly diagnosed head and neck cancer patients. Methods: This cohort study recruited newly diagnosed head and neck cancer patients (N=547) in three otorhinolaryngology clinics including a large urban community hospital, a VA medical center, and a large university medical center. Participants completed written surveys and chart audits were conducted. The independent variables were race (white versus all others) and socioeconomic status as measured by educational level (high school or less versus some college or more) and income (mean income for census tract). Control variables included age, gender, smoking status, alcohol problem, tumor site, tumor stage, and comorbidities. Treatments were not included in the final models because they were correlated with one another, and with cancer site and stage, and all patients received treatment according to standard protocols. Kaplan-Meier plots, univariate and multivariate Cox Proportional Hazards Models were used to determine the relationship between race/ethnicity and socioeconomic status and the dependent variable of all-cause survival. Results: Fourteen percent were non-white (8% African American, 3% Native American, and 3% Hispanic/Latino). Forty-nine percent had completed a high school education or less, and the median income level for census tract was $43,514 per year (range $11,223 - $156,712). The mean age of the subjects was 59 years old and 78% were male. About 56% were former smokers and 26% were current smokers. One quarter screened positive for problem drinking. Most were stage III or IV (79%), and had cancer of the pharynx (oro-, hypo-, naso-pharynx or unknown primary) (52%), while 25% had cancer of the larynx and 23% had cancer of the oral cavity. Moderate or severe comorbidities were present in 34% of the population. The 2-year all-cause death rate was 28%. Both univariate and multivariate Cox Proportional Hazards Models revealed significantly elevated hazard ratios for high school education or less (HR 1.5, 95% CI 1.1-2.0) and income below $35,000 (HR 1.4, 95% CI 1.0-1.9). Older age, current and former smoking, oral cancer site, stage III/IV cancers, and moderate to severe comorbidities also predicted poorer survival. Race/ethnicity, gender, and alcohol problem were not associated with survival in the univariate models and therefore not included in the multivariate analyses. Conclusions: Head and neck cancer patients with lower socioeconomic status are at risk for lower all cause survival. Those with lower educational levels may need targeted materials such as videotapes and phone calls to reinforce teaching. Those with lower incomes may benefit from intensive referrals to community resources. More intensive follow-up of patients of lower socioeconomic status may be warranted.
ed experiences are likely to only include a small proportion of the total population. Looking carefully at statistical reports in many published studies reveals that usually, only a proportion of the total population are used for outcome analysis, which could introduce further biases. **Objectives:** To quantify the possible errors introduced by only reporting on a small proportion of the total population with Head and Neck Cancer (HNSCC). To define the actual correlation and representation between total population statistics and the cohort of patients to be reported on in a population based study. **Materials and Methods:** Computerized database was created in access inter-relational database with comprehensive data entry. This included all patients diagnosed with HNSCC in the period from 1960 to 2005. All the Head and Neck database listings were reviewed to ensure that all patients' names were captured. Data captured included Age at diagnosis, Gender, Presenting Symptoms & Signs, Investigations (findings), Living/disease status at last F/U (+ cause of death), Tumour location, size, Histology, Grade, TNM classification, Treatment modality such as surgery, chemotherapy, radiotherapy, its dose and intent (radical/adjuvant/palliative), Treatment Toxicities, Social Habits (tobacco, EtOH) and occupational exposure. Quality assurance audits were carried out on the charts. Data were entered into the computer database to allow for analysis. This was compared with Provincial database which included limited information including demographics, treatment and survival statistics. **Results:** During the period of 1960 to 2005 a total of 6727 patients were registered in the Provincial database. 1137 arisen in the Oral Cavity (excluding Lips), 635 in the Lips, 256 Nasopharynx, 1272 in the Oropharynx, 379 in the Hypopharynx, 1890 in the Larynx, 300 in the Salivary Glands, 251 in the Sinuses, 6 in the Ear, in 626 site unspecified. Reported incidence of second tumours were 6 primary tumours in 1 patient, 5 in 4 patients, 4 in 15 patients, 3 in 68 patients, 2 in 523 patients (8%) and 1 in 614 patients (91%). Only 1330 (19.6%) patients were eligible to be included in the comprehensive database. These were the patients who had adequate reliable information to allow meaningful statistical analysis. Site and various parameters distribution was significantly different between the 2 databases. The discrepancy could result in as much error as 20%. Detailed analysis will be presented. **Conclusion:** That study highlights the added deficiency in lymph node metastasis based on clinical and pathological features presented by patients with SCC of the UADT according to its primary site. Methods: A multicenter prospective study of 1074 consecutive patients with SCC of the UADT treated from July 2002 to June 2007 was performed. For seven primary tumor sites of the upper aero-digestive tract, clinical and pathological data were compared between patients with and without LN metastasis by univariate and logistic regression analysis. Predictive independent variables were used to calculate the individual risk of LN metastasis in percentage, for each primary SCC site. We focused the risk threshold of 20%, which indicates elective neck dissection in surgical practice. Results: for the SCC of the (1) laryngeal region there was no independent predictive variable of LN metastasis. For the (2) T1 SCC of the tongue, tumor thickness was an independent predictive variable (exp&#223;9.7, P = 0.03) and thickness deeper than 1cm predicted an individual risk higher than 20% of LN spread. In the other (3) oral cavity sites, tumor thickness (exp&#223;1.5 each centimeter, P = 0.007) and presence of lymphatic invasion (exp&#223;6.7, P = 0.001) were predictive: individual risk for group 3 patients begins in 25% even in the absence of lymphatic invasion and smallest tumor thickness. In the (4) Oropharynx and (5) hypopharynx SCC only the presence of lymphatic invasion (exp&#223;59.1, P = 0.001 and exp&#223;8.0, P = 0.004 respectively) was predictive of LN metastasis but even patients without lymphatic invasion had already more than 20% (52% and 60%) of risk. For (6) glottic SCC the presence of lymphatic invasion (exp&#223;42.4, P = 0.004) and tumor size (exp&#223;1.3 each centimeter, P = 0.035) were independent predictive variables: a patient with glottic SCC without lymphatic invasion and tumor size larger than 3.7cm has an individual risk higher than 20% of LN spread; and in the presence of lymphatic invasion, tumor size larger than 1cm has a risk higher than 20%. In the other (7) laryngeal regions the same variables were predictive (presence of lymphatic invasion, exp&#223;4.3, P = 0.001; tumor size, exp&#223;1.3 each centimeter, P = 0.035) of a patient with SCC without lymphatic invasion and tumor size smaller than 0.5cm has an individual risk of LN metastasis below 20%. **Conclusions:** for all patients with oral cavity, oropharynx and hypopharynx SCC, T1 tumor of the tongue deeper than 1cm, exclusively glottic region SCC with lymphatic invasion and larger than 1cm, the predicted individual risk of LN metastasis were higher than 20%. In contrast, considering other laryngeal SCC, elective neck dissection may be avoided in patients with tumor without lymphatic invasion and smaller than 0.5cm. **S170:** SECOND PRIMARY TUMORS IN LARYNGEAL SCC ARE NOT ASSOCIATED WITH ADVERSE OVERALL SURVIVAL R.D. Forhadie1, A. Salardiini2, J.L. Yang3, C.G. Rees4, P.J. Russell5, R.Smees6, 1Prince of Wales Hospital, Sydney, Australia; 2UNSW, Yales University, New Haven, CT; 3UNSW, Sydney, Australia; 4Prince of Wales Hospital, UNSW, Sydney, Australia **Background:** Head and Neck Squamous Cell Carcinomas (HNSCCs) remain a public health scourge and despite recent advances, continue to be associated with poor prognosis. Second Primary Tumors (SPTs) have been implicated as a major factor. The aim of this study was to examine the prognostic impact of SPTs on survival in patients with SCC of the larynx (1967-2007). Minimum follow up was three years. Last patients considered for the study commenced treatment in 2004. The clinical and demographic data were analyzed to establish: the incidence of SPTs; the time-lag in diagnosis of the SPTs from the index tumor; the impact on survival; and the estimation of risk in this patient population. **Results:** During the median follow up of 65 + 3.2 (range: 1-380) months, 143 (14.5%) patients developed upper aerodigestive tract SPTs, of which 83 (5.8%) were HNSCCs, 56 (5.7%) were lung, and 4 (0.4%) were esophageal SPTs. Survival analysis demonstrated unexpected but clear superior overall survival rates for the patients with upper aerodigestive tract SPTs (P<0.008). This effect was most pronounced in those with HNSCC-SPTs (P<0.001) when compared with patients with no SPTs. Patients with synchronous SPTs had a poorer overall survival (P<0.001). The average annual risk of developing an upper aerodigestive tract SPT was 2.4% in this patient cohort. The results of this study suggest that HNSCC-SPT should not be viewed as an adverse prognostic factor. Reclassifications of upper aerodigestive tract SPTs into HNSCC-SPT and non HNSCC-SPT would better reflect their clinical behaviour and overall prognosis.
As can be seen in table 1, the total population of patients was 672. Mean follow-up was 10 years with a range of 3-25 years; the incidence of follow-up was around 0.75% per year for the total population. Taking into consideration that 70% of the total number of patients that survived their first primary; the incidence of second primary in patients who are cured from the first primary averaged around 1% per year. The incidences of subsequent primaries are shown in table 1.

Table 1
Total population (n=672)
1-primary 6115 (90.9%)
2-primaries 523 (7.8%)
3-primaries 68 (1%)
4-primaries 16 (0.2%)
5-primaries 4 (0.1%)
6-primaries 1 (0.0%)

Conclusions: These results support the fact that the incidence of second and subsequent primaries might have been underestimated in the literature. That should be taken into consideration in the future design of randomized trials and planning of sample size.

CLINICAL: ORAL CAVITY

S172: MARGINAL MANDIBLECTOMY FOR BUCCAL SULCUS CANCERS: 10 YEAR INSTITUTIONAL EXPERIENCE K.A.Patik 1, B.C.Shah 1, M.S.Deshpande 1, Tata Memorial Hospital, Mumbai India

Background: Marginal mandibullectomy is a mandible preserving procedure for resection of the oral cancer involving the mandible superficially or coming close to it thereby necessitating a mandibular resection for adequacy of margins. Most of the published papers from the west deal with its application in floor of mouth cancers. The present study was aimed to evaluate the oncological outcome of marginal mandibullectomy in gingivobuccal cancer and compare it with that of tongue/floor of mouth cancer.

Material and Methods: Charts of all 179 patients who underwent marginal mandibullectomy between 1993 and 2003 at Tata Memorial Hospital were reviewed. Of these, 161 underwent marginal mandibullectomy for invasive squamous cell carcinoma (SCC) and were followed up for a median period of 30.6 months. Oncological outcomes in terms of disease control and cause specific survival for the gingivobuccal and tongue/floor of mouth cancers were compared in independent impacts of site of tumor, microscopic bone invasion, T and N stage, grade of differentiation, adjuvant radiotherapy on the locoregional control and cause specific survival. were evaluated using Cox Proportional Hazard model.

Results: 137 marginal mandibullectomies were done for SCC in buccal sulcus and 24 for floor of mouth SCC in 132 (82%) males and 29 (18%) females of mean age 50.4+10.2 years. Clinically 10 (6.2%) patients had T1 cancer, 85 (52.8%), T2, 36 (22.4%) T3 and 28 (17.4%) T4 tumor because of involvement of overlying skin. Bone was microscopically involved in 13 (8.1%) cases and margin of excision showed tumor in 12 (7.5%) cases, but both of these did not have any influence on locoregional failure or cause specific survival. 42 (26.1%) patients developed recurrent disease. The 2-year and 5-year disease free survival rates were 76.1% and 62.9%, respectively. Primary site was the commonest site of failure in 33 cases (20.5%). The local failure free survival at the end of 2 and 5 years was 84.9% and 71.4%, respectively. At the time of last contact 121 (75.2%) patients were alive and disease free, 10 (6.2%) had died of unrelated causes. Rest were either alive with unsalvageable disease or had succumbed to it. Cause specific survival at 2 and 5 years were 85.6% and 72.6% respectively. Cause specific survival at 5 years was significantly better for gingivobuccal cancer than floor of mouth cancer (76.1 Vs 42.7; p=0.041) but there was no difference in the locoregional control rates at 5 years (72.2 Vs 81.3; p=NS). On multivariate analysis patients with floor of mouth cancer undergoing marginal mandibullectomy were at three times higher risk of dying of disease than those with gingivobuccal cancer but the site did not have an independent influence on disease specific survival.

Conclusion: In carefully selected patients, marginal mandibullectomy is an oncologically safe procedure to achieve good local control and survival in gingivo-buccal cancer which is comparable to that in floor of mouth cancer, if not better.

S173: CARCINOMA OF THE BUCCAL MUCOSA: PRESENTATION, TREATMENTS, AND PATTERNS OF FAILURE G.V.Bachar 1, D.Goldstein 1, J.Lea 1, G.Bruch-Andrey 1, G.Lockwood2, D.Brown 1, R.Moukarbel 1, R.Gilbert 1, P.Gullane 1, J.Irish 1, Princess Margaret Hospital-Otolaryngology Head and Neck Surgery, Toronto, ON, Canada; 2Princess Margaret Hospital, Toronto, ON, Canada

Objective: To review the clinical outcomes of patients with buccal carcinoma treated at the Princess Margaret Hospital. Methods: A retrospective chart review of patients treated for buccal carcinoma between 1994-2004 was performed. Ninety-nine patients with newly diagnosed and previously untreated squamous cell carcinoma of the buccal mucosa were included. Demographic, clinical and pathological parameters were identified and correlated with outcomes. Results: The patient cohort consisted of 57 males and 42 females. Surgery was the primary treatment in 54 patients, whereas 45 patients were treated with primary radiotherapy. Twenty patients were treated with postoperative radiotherapy. Median follow-up was 3.7 years. The 3 and 5 year overall survival rate was 69% and 58% respectively. The 5 year disease free survival (DFS) rate was 42%. The local and regional recurrence rate was 30% and 16%, respectively. The presence of regional disease significantly decreased the 5 year DFS rate from 73% to 29%. Conclusions: Carcinoma of the buccal mucosa is an aggressive disease, characterized by a high rate of locoregional failure. Transoral wide excision is an adequate treatment for early stage lesions however a combined approach and an elective neck dissection should be considered in advanced lesions.

S174: IDENTIFYING RISK FACTORS FOR POST OPERATIVE CARDIOVASCULAR AND RESPIRATORY COMPLICATIONS AFTER MAJOR ORAL CANCER SURGERY J.K.Dillon 1, S.Liu 1, C.Patel 1, B.L.Schmidt 1, 1University of California, San Francisco, San Francisco, CA

Objective: Our aim is to identify predictors for cardiovascular and respiratory complications following surgery for oral squamous cell carcinoma (OSCC). The predictor model is comprised of the revised Goldman criteria with additional risk factors pertinent to surgery of OSCC. Methods: We performed a retrospective review of 69 patients with complete records who were treated at UCSF by the OMFS oncology service for primary oral cancer between 2003-2007. The Goldman six-point criteria: (high risk surgery, ischemic heart disease, cerebrovascular accident, congestive heart failure, diabetes, pre-operative creatinine level) were applied to our cohort as a predictor model for post-operative complications. Additional parameters for the predictor model include: location of primary tumor, exact procedure performed, hypertension, history of cardiac procedures, current use of beta-blockers, hypercholesterolemia, tobacco and alcohol history, transeosphyageal echocardiogram, duration of hospital stay, and duration of ICU stay. Cardiovascular complications were defined as post-operative episodes of arrhythmia, management with beta-blockers, and myocardial infarct. Respiratory complications were defined as pneumonia, re-intubation during hospital stay, and respiratory distress. Univariate analyses using the Chi-squared test were performed. Results: There were 69 patients in our study.
While margin status in oral squamous cell carcinoma (OSCC) depends heavily on locoregional control. In this study, we sought to determine the independent prognosticators for local tumor control, disease-specific survival (DSS) and overall survival (OS) rates in a series of OSCC patients undergoing radical surgery. Methods: We retrospectively reviewed 827 consecutive OSCC patients from January 1998 to March 2005 undergoing radical surgery. Postoperative radiotherapy was performed in patients with pT4 tumors, positive lymph node(s), or close margins (< 4 mm). Local control rates and survivals were plotted using the Kaplan-Meier method. Results: On multivariate analysis (MVA), unfavorable prognostic factors for local control were pathological margins < 7 mm (P < .001), pathological tumor depth ≥ 26.5 mm (P < .001), pathological positive lymph node(s) (P = .001), and the presence of betel quid chewing (P = .012). The same predictors, the only exception being betel quid chewing, were independently associated with DSS and OS in MVA. A prognostic scoring system was formulated by summing up the four significant factors to control outcomes from MVA. Patients with scores of 3-4 had a significantly poorer local control rate compared to patients with scores of 0-2 (score 3 vs. score 0-2: P < .001; score 4 vs. score 0-2: P < .001). Conclusions: Taken together, our data suggest that pathological margins, pathological tumor depth and pathological lymph node status are major independent prognosticators not only for local tumor control, but also for DSS and OS.

S175: FACTORS CONTRIBUTING NEED OF TRACHEOSTOMY AND STRATEGIES TO OVERCOME THAT IN ORAL AND OROPHARYNGEAL CANCER SURGERY
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Objective: To evaluate factors influencing the need of tracheostomy in patients undergoing tumor resection for oral and oropharyngeal cancer surgery. The study was designed to define various factors affecting need of tracheostomy or prolonged intubation in 486 consecutive patients with oral and oropharyngeal cancer undergoing major surgery. It also aimed to define effective strategies to prevent and avoid tracheostomy or prolonged intubation by risk analysis.

Methods: The medical records of 486 consecutive patients of head and neck cancer undergoing surgery for oral and oropharyngeal cancers were studied. Out of them, 210 patients underwent composite resections and were found to have presence of various factors contributing to the need of tracheostomy or prolonged intubation on conventional grounds and were analyzed in detail. The factors analyzed were age, previous surgery, previous radiotherapy, extent of surgery, decreased mouth opening, extent of mandibular resection and mode of reconstruction. Further these factors were divided in major and minor as per subgroup analysis. Effective strategies to avoid tracheostomy or prolonged intubation included awake nasotracheal intubation, meticulous dissection, surgical strategies for prevention of tongue fall and laryngeal suspension.

Results: Out of 210 patients, 7 underwent segmental, 122 hemi, 3 extended hemi, 16 central arch mandibulectomy. Twenty two patients underwent paramedian mandibulotomy. One hundred eighty eight patients underwent pediculated myocutaneous flap reconstructions and 38 underwent free microvascular flap reconstruction. In all the cases the trachea was extubated in the immediate postoperative period. Only eight (3.8%) patients required tracheostomy for their perioperative management. In none of the cases, elective tracheostomy was performed before surgery for the maintenance of the airway for anesthesia. Elective tracheostomies were done in 6 cases during surgery. Two cases required tracheostomies in post operative phase. The analysis showed that major important factors to predict the need for tracheostomy or prolonged intubation were previous radiotherapy, resection encompassing more than one head and neck region, central arch mandibulectomy/Extended hemi mandibulectomy, bilateral neck dissection, Bulky flaps and regular pedicled flaps with outer intact bony coverage. Minor factors were age, past history of radiotherapy, trismus and previous surgery. All the patients in whom tracheostomies were anticipated had presence of at least two major and one minor factor. Conclusion: Oral and oropharyngeal cancer patients undergoing major surgery have a potentially difficult airway management but, if managed properly during perioperative period, morbidity and mortality can be reduced or avoided. Oral cancer and oropharyngeal cancer patients have an increased risk of development of airway compromise post surgery. Therefore, preoperative risk assessment, early use of a tracheostomy or prolonged intubation by practicing various effective methods, need for tracheostomy can be predicted by using the risk analysis system. Keywords: Oral and oropharyngeal cancer, tracheostomy, prolonged intubation, risk analysis system, airway management.

S176: ANALYSIS OF RISK FACTORS PREDICTIVE OF LOCAL TUMOR CONTROL IN ORAL CAVITY CANCER
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Objective of the Study: Survival in oral cavity squamous cell carcinoma (OSCC) depends heavily on locoregional control. In this study, we sought to determine the independent prognosticators for local tumor control, disease-specific survival (DSS) and overall survival (OS) rates in a series of OSCC patients undergoing radical surgery. Methods: We retrospectively reviewed 827 consecutive OSCC patients from January 1998 to March 2005 undergoing radical surgery. Postoperative radiotherapy was performed in patients with pT4 tumors, positive lymph node(s), or close margins (< 4 mm). Local control rates and survivals were plotted using the Kaplan-Meier method. Results: On multivariate analysis (MVA), unfavorable prognostic factors for local control were pathological margins < 7 mm (P < .001), pathological tumor depth ≥ 26.5 mm (P < .001), pathological positive lymph node(s) (P = .001), and the presence of betel quid chewing (P = .012). The same predictors, the only exception being betel quid chewing, were independently associated with DSS and OS in MVA. A prognostic scoring system was formulated by summing up the four significant factors to control outcomes from MVA. Patients with scores of 3-4 had a significantly poorer local control rate compared to patients with scores of 0-2 (score 3 vs. score 0-2: P < .001; score 4 vs. score 0-2: P < .001). Conclusions: Taken together, our data suggest that pathological margins, pathological tumor depth and pathological lymph node status are major independent prognosticators not only for local tumor control, but also for DSS and OS.
S178: MANAGEMENT OF THE CLINICALLY NONEC IN ORAL AND OROPHARYNGEAL CARCINOMA IN SCOTLAND
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Background: The management of the clinically N0 (cN0) neck in patients with oral and oropharyngeal squamous cell carcinomas (SCC) remains controversial. Factors such as patient comorbidity, different personal opinions, pathological and other factors modify the treatment decisions. Aim: Our primary aim was to determine the management of the cN0 neck in oral and oropharyngeal SCC patients in different institutions in Scotland. The secondary aim was to evaluate the outcome of the patients who had not undergone any treatment of the neck in comparison with those who had elective neck treatment, and also examine factors relating to overall survival in this population.

Patients and Methods: Based on a prospective head and neck cancer audit carried out in Scotland between September 1999 and October 2001, we focused on the management of N0 neck in patients with oral or oropharyngeal SCC. Out of total of 1910 patients in the audit, 364 patients with oral or oropharyngeal SCC and cN0 neck were treated with planned curative outcome. The overall survival data was available up to a minimum of 5 years, and a detailed clinical follow-up to a minimum of 18 months.

Results: One hundred patients had no treatment to the neck (observation group). A total of 112 patients received prophylactic neck chemotherapy without elective neck dissection (END). END was performed for 152 patients (of which 23 were bilateral) and 63 of them received postoperative radiotherapy. Histopathological examination revealed metastases in only 16% of the dissection specimens. In the observation group, 6 patients (6%) had a recurrence of the neck without any recurrence on the primary site. For the rest of the patients who had any sort of elective neck treatment, the respective figure was also 6% (15/256). Neck imaging was recorded in 186 patients only. Conclusion: There is a wide variation in the management of the cN0 within Scotland. The use of imaging for diagnosis is also variable. A surprisingly low percentage of patients proved to have had metastasis on pathological examination. Despite variations in treatment, neck recurrence was relatively uncommon. This audit demonstrates the need for more defined protocols for the management of the cN0.

S179: METASTASES TO LEVEL IIb IN ORAL CAVITY CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Objective: To determine the prevalence of level IIb metastases in previously untreated squamous cell carcinoma of the oral cavity. Methods: A systematic review of the literature and review of the Princess Margaret Hospital experience was performed. Two independent reviewers screened abstracts and full text papers deemed potentially relevant. Data was pooled using a fixed effects model. Results: Two independent reviewers screened 729 abstracts, and 177 full text papers (Kappa statistic 0.81 & 1.0, respectively), with consensus for inclusion reached on 9 full text papers. A total of 332 patients were included in the analysis. Twenty patients had level IIb metastases (Mean 6%, Range 0-10.4%). The pooled percentage of level IIb metastases was 6.0% (95% CI 0.22-22.3%). Only 3 patients with level IIb metastases had isolated nodal disease. Eighty-five percent of those with level IIb metastases had additional nodal disease (95% CI 64.94-8.8%). with IIa being a common denominator among all. There were no level IIb metastases among our series of 40 patients at Princess Margaret Hospital.

Conclusions: Level IIb metastases is uncommon in previously untreated squamous cell carcinoma of the oral cavity [6]. In addition, isolated level IIb nodal disease is uncommon. Eighty-five percent of those with level IIb metastases harbour associated nodal disease, with a strong preponderance for level IIa. Coupling the risk of post operative shoulder dysfunction with the low prevalence of level IIb metastases brings in to question the need for routine dissection of level IIb. While a change in practice may be on the horizon, further data from a large prospective multi-institutional cohort study is recommended.
A retrospective analysis of all the patients who underwent mandibu-
lar tumour resection and reconstruction with a composite free flap and use of the unilock 2.0 mm system over a 3 year period at the University Hospital Birmingham, UK. 

**Results:** A total of 35 patients had mandibular reconstruction with a composite free flap. The results of the study will be presented.

**Conclusions:** The unilock 2.0 mm reconstruction plates are easier to use, bend and their lower profile has resulted in no plate exposures. The facial profile was excellent. There were no plate fractures. This plating system also allows insertion of implants without the need for plate removal.

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**S182: MANDIBULAR CONDYLE RECONSTRUCTION WITH FIBULAR FREE TISSUE TRANSFER**

**S.S. Hamilton¹, E.J. Moore¹, ¹Mayo Clinic, Rochester, MN**

**Objective:** The use of fibular free flap tissue for reconstruction of the mandible is a well accepted procedure. However, a consensus has yet to be reached regarding the best method for reconstruction of the condyle when it also must be resected. Techniques that have been attempted to reconstruct the condyle include costal chondral grafts, titanium temporomandibular joint prostheses, calvarial bone grafts, attachment of the resected condyle to the end of a graft, and use of acellular dermal matrix material as a condylar cap. Another option is placing the carved end of the fibular graft into the glenoid fossa. We aim to describe how this procedure is performed and the results of a series of seven cases completed at the Mayo Clinic.

**Methods:** Seven patients underwent partial mandibulectomies which included the condyle at the Mayo Clinic between November 2005 and January 2007. A fibular free flap osteocutaneous graft was used to reconstruct the defect in all seven cases. The condyle was reconstructed by inserting the contoured end of the fibular tissue into the glenoid fossa after it had been covered by soft tissue associated with the flap. Patients were placed in post-operative occlusion for one week followed by six weeks of a soft diet. Mild post-operative trismus resolved with use of the Therabite system and early mobilization of the joint. The patients were followed-up at regular intervals with attention being paid to recurrence, function, and cosmesis.

**Results:** All seven patients that underwent this procedure were male. The average age of the patients was 59 years old. All patients underwent successful resections with no intraoperative complications. One patient experienced a submandibular hematoma which required surgical intervention. Four experienced mild facial nerve paralysis which resolved over time. Follow-up time ranged from 8 to 25 months with a mean of 16 months. There were no lasting problems with trismus, malocclusion or difficulty with mastication. No ankylosis was noted. Additional procedures performed included left gold weight placement, abdominal dermal fat graft reconstruction of a cheek soft tissue deficit, lingual frenotomy and myringotomy. Five of the seven patients underwent postoperative radiation, experiencing no associated morbidities. Three experienced recurrences in the ipsilateral parapharynx, ipsilateral maxillary sinus and contralateral mandible. One patient experienced occasional joint locking, but without trismus. The described technique of condylar reconstruction following a hemimandibulectomy provides excellent results with regards to mandible function, cosmesis, and morbidity. Rate of recurrence is comparable to that of other techniques. One distinct advantage of this procedure is that the fibular flap is vascular, thus it responds better to radiation treatment than avascular approaches. One critique of this technique in the past has been the possibility of joint fixation and trismus. However, neither was seen in this series. An explanation for this is the fact that the patients went through early mobilization and rehabilitation exercises. This leads to the possibility of future studies of the effects of rehabilitative exercises on ankylosis following this procedure.

**S183: STEREOLITHOGRAPHIC BIOMODELLING IN MANDIBULAR RECONSTRUCTION**

H. Seikaly¹, J. Zhu¹, D. O'Connell¹, D. Cote¹, A.M. Mylnarek¹, K.A. Al-Qahtani¹, N. Rizk¹, K. Ansari¹, J. Harris¹, J. Wolfard¹

**1University of Alberta, Edmonton, AB, Canada**

**Introduction:** Medical rapid prototyping allows anatomic data from three dimensional computer tomography studies to be generated into replicas of the patient’s anatomy. The clinical utility of this technology has been actively investigated in multiple surgical disciplines, including neurosurgery, orthopedics, maxillofacial and vascular surgery. In head and neck reconstruc-
tion, it has been suggested that it could be potentially beneficial for pre-surgical planning and intraoperative guidance. **Objective:** To evaluate the utility of stereolithographic biomodels in mandibular reconstruction in the laboratory setting. **Methods:** Using medical rapid prototyping, thirty sets of anatomic models were created based on CT images of a patient affected by a tumor involving the mandible and undergoing a resec-
tion of the anterior mandibular segment form angle to angle. Ten of the models were of the complete craniofacial skeleton. Another 20 copies were incomplete, lacking a segment of the mandible from angle to angle. Ten experienced reconstructive surgeons and ten novice surgical trainees receive the incomplete models en surgeons randomly received also the complete model of the skeleton as a guide. Each participant was asked to bend a titanium reconstruction plate to simulate the native mandible. The end product was evaluated on the basis of its accuracy, with a focus on the angle and 1 year it was 1% and 10% respectively. **Results:** The data showed that plates bent with the aid of a complete bio-model were more accurate that their counterpart. The difference was more pronounced with the surgical trainees. **Conclusions:** Rapid prototype aids the reconstructive surgeon in creating a more accurate neo-mandible. It also has potential utility in surgical education.

**S184: SURVIVAL AND FUNCTIONAL OUTCOMES OF BASE OF TONGUE CANCER PATIENTS TREATED WITH PRIMARY SURGERY AND RECONSTRUCTION**

H. Seikaly¹, D.A. O'Connell¹, J. Rieger¹, D. Williams¹, K. Al-Qahtani¹, A.M. Mylnarek¹, N. Rizk¹, K. Ansari¹, J.R. Harris¹, ¹University of Alberta, Edmonton, AB, Canada; ²University of Alberta, Edmonton, AB, Canada

**Introduction:** Head and neck oncologists are often confronted with the difficult challenge of balancing cancer cure with the preservation of func-
tion, cosmesis, and quality of life when deciding the patients best treatment protocol. This task is especially difficult for cancer of the base of tongue as this organ is intimately involved with the complex functions of respiration, deglutition and speech production. Treatment of advanced stage cancers of the base of tongue generally requires a combination of surgery, radiation and chemotherapy, but the order and extent in which these different modalities are employed continues to be controversial. The two widely accepted treatment regimens include: 1) primary surgery and reconstruction followed by radiation and chemotherapy, and 2) organ preservation with primary concurrent chemo-radiotherapy followed by surgery for salvage or neck dis-
ease. Assuming that both of these regimens offer acceptable cancer control rates the final treatment recommendation would have to depend on the protocol’s functional outcomes. Our program continues to offer both treatment op-
tions to patients with advanced base of tongue cancer. We have also developed a method of reconstruction that restores the bulk and mobil-
ity of this organ in an attempt to preserve its complex functions of respira-
tion, deglutition and speech production. **Purpose:** The purpose of this presentation is to report the survival and functional outcomes of a prospec-
tive cohort of patients with base of tongue cancer treated with primary sur-
gery. **Methods:** 66 consecutive patients treated between 1998 and 2003 for squamous cell carcinoma of the base of tongue were followed prospectively through our Multidisciplinary Head and Neck Surgery Reconstruction Clinic. All patients had a minimum follow up of 3 years. Swallowing was assessed with videofluoroscopy and a diet questionnaire. Speech was assessed perceptually and aeromechanically. All assessments were performed at 4 points in time (preoperative and 1-month, 6-months, and 1-year postoperative). **Results:** The average age of the cohort was 56.8. 56 (85%) were male and 10 (15%) were female. 64 (97%) patients had postoperative adjunct treatment. 3 (5%) patients had stage 1 - 2 and 63 (95%) had stage 3-4 disease. The disease specific sur-
vival was 87% at 3 years and 78% at 5 years. Local control was achieved in 94% of patients. 7.5% had distal metastasis and 7.5% developed sec-
ond primaries. Restoration of speech function was achieved, with normal perceptual, acoustic and aeromechanical speech outcomes for all patients across all assessment times. The swallowing results reveal that timely restoration of swallowing function was achieved for the majority (91%) of patients at 1 year. The rate of gastrostomy tube placement rate at 1 month and 1 year were 13% and 10% respectively. **Conclusion:** Primary surgical 
treatment of advanced BOT cancer continues to offer excellent local con-
trol, disease specific survival and functional outcomes.

**S185: PERIOPERATIVE AIRWAY MANAGEMENT IN PATIENTS RECEIVING ORAL CAVITY FREE FLAPS: CAN TRACHEOTOMY BE SAFELY AVOIDED?**

M.G. Moore¹, A. Bhavy¹, D. Francis¹, B. Yueh², N. Futran¹

¹University of Washington, Seattle, WA; ²University of Minnesota, Minneapolis, MN

**Objectives:** Traditional airway management for patients receiving free tissue transfer for reconstruction of large defects of the oral cavity involves elective tracheotomy at the time of the surgical intervention. While this provides a secure airway and is technically straightforward, it is associated with additional potential morbidity and may not be necessary for all patients. We set out to evaluate the influence of upfront tracheotomy on peri-

Brain metastases in patients with cancer of the oral cavity or oropharynx are often treated with surgical resection. Some patients also require pre-op or post-op tracheostomy. While this can help secure the airway, it is associated with additional potential morbidity and may not be necessary for all patients. Whole brain radiotherapy (WBRT) has been used to treat patients with brain metastases. It is well known that radiation can cause toxicities to the brain and other organs. In addition, patients may receive other treatments, such as chemotherapy or surgery, at the same time. The main goal of this study was to determine the toxicity of whole brain radiotherapy, including its effect on the brain and other organs. The study was done in collaboration with the Mayo Clinic and involved patients who received WBRT. The results were analyzed using statistical methods. The study concluded that whole brain radiotherapy is safe and effective in treating brain metastases. However, it also showed that the treatment had some side effects, such as nausea, vomiting, and fatigue. The study also showed that the treatment was effective in reducing the size of the brain tumors. Overall, the study demonstrated that whole brain radiotherapy is a safe and effective treatment for brain metastases in patients with cancer of the oral cavity or oropharynx.
operative outcomes of patients receiving free flap reconstruction in an attempt to determine which patients should receive a tracheotomy as part of their surgical management. Methods: A retrospective medical record review was performed on all patients receiving free tissue transfer to reconstruct defects of the oral cavity between March of 2006 and October of 2007. Patient, tumor and treatment related variables were recorded. Each patient was either managed with nasotracheal intubation (NTI) or elective tracheotomy. Perioperative outcomes included the length of mechanical ventilation, total ICU stay, total hospital stay, feeding tube dependence at discharge, and airway related complications. Results: A total of 58 patients were studied (37 had nasotracheal intubation and 21 had upfront tracheotomy). There was no difference in the mean age of the two groups or in the tumor T-stages. A higher percentage of patients receiving elective tracheotomy had a history of alcohol abuse (44% vs 6%, p<0.05). A higher percentage of the NTI group had mandible resection and reconstruction as part of their procedure (74% vs 52%, p<0.05). The mean total hospital stay was prolonged in the tracheotomy group (12.4 days vs 8.4 days, p<0.05). In addition, more patients in the tracheotomy group were dependent on their feeding tube at the time of discharge (76% vs 19%, p<0.05). In a multivariate analysis, placement of a tracheotomy, preoperative alcohol use, and advanced tumor T-stage were all correlated with longer hospital stays (p<0.05). With regards to feeding tube dependence at discharge, advanced age and tracheotomy were found to be independent risk factors (p<0.05). No patients in the NTI group required conversion to tracheotomy or re-intubation over the course of their hospitalization. Conclusions: The use of nasotracheal intubation is a safe alternative to elective tracheotomy for perioperative management of select patients receiving free flap reconstruction of oral cavity defects. By avoiding tracheotomy, the length of hospital stay and the likelihood of feeding tube dependence may be reduced.

S186: VERSATILITY OF THE ALT FLAP IN HEAD AND NECK RECONSTRUCTION

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Background: The anterolateral thigh (ALT) flap, first described by Song, is now worldwide proclaimed as the workhorse in microvascular Head and Neck reconstruction due to its multiple virtues. Essentially, it is reliable, has minimal morbidity and offers multiple applications in a variety of complex defects. In this paper we focus on the last property, being that we have used this flap to reconstruct almost every area in the head and neck region. Methods: 14 ALT flaps were performed in 13 patients from April 2006 to December 2007. Results: The success rate was 100% with no partial loss of any flap. All donor sites were closed primarily, except for two cases that required a skin graft. Nine cases were strictly perforator flaps, the other five included at least a portion of the vastus lateralis muscle. There were no major complications. We reconstructed 5 complex skull base defects, 2 total pharyngectomies, 5 oral cavity and maxillary resections, and 2 cases of soft tissue coverage. Conclusions: We found this flap to be highly reliable and useful in the reconstruction of a variety of head and neck defects and it is nowadays our first choice, except in small oral cavity defects were this flap may be too bulky.

S187: FREE POSTERIOR Tibial Flap FOR HEAD AND NECK RECONSTRUCTION AFTER TUMOR RESECTION

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Objective: A clinical review was conducted to evaluate the efficacy of free posterior tibial flap for reconstruction of the head and neck defect after tumor resection. Method: All posterior tibial flaps performed in our institution for head and neck reconstruction were included. The age and gender of the patients, the site of the primary tumor, results of flap transfer, and donor site morbidity were analyzed. Results: Between January 2006 and November 2007, 20 patients underwent primary reconstruction with free posterior tibial flap for soft tissue defect immediately after surgical resection of the head and neck tumor. There were 18 men and 2 women whose age ranged between 34 and 83 years. The flap was used to repair the oral cavity mucosal defect after tumor resection in 19 cases and as an external skin covering for 2 cases. A pedicled supraclavicular artery flap is an excellent flap option for poor microvascular candidates or patients who do not wish to have a free tissue transfer. This thin flap is easy and quick to harvest, has a reliable pedicle, and has minimal donor site morbidity.

S188: SUPRACLAVICULAR ARTERY FLAP: A VERSATILE REGIONAL FLAP ALTERNATIVE FOR HEAD AND NECK ONCOLOGIC RECONSTRUCTION

V.Liu1, P.L.Friedlander1, E.Chiu1, 1Tulane University Health Sciences Center, New Orleans, LA

Objective: Soft tissue oncologic reconstruction of the head and neck region may require local, regional, or free flaps after tumor ablation. Regional muscle flaps (pectoralis major, deltopectoral, trapezius) are not only bulky, but have associated donor site morbidity. Microsurgical free flaps (forearm, anterolateral thigh, parascapular, abdominal) require technical expertise and increased operative time (Table I). The pedicled supraclavicular artery flap, initially described for skin resurfacing after burn/trauma scar contracture release, is a thin, fasciocutaneous flap that can be harvested easily and quickly. We demonstrate that this axial flap is also an excellent regional flap alternative for reconstructing oncologic neck and lower third facial defects. Methods: Tumor ablation defects of the neck and lower face (partial and circumferential pharyngeal, mandible, and oral cavity) were reconstructed using a pedicled supraclavicular artery rotation flap. All pedicle vessels were pre-operatively mapped using a handheld Doppler probe. Flap design was based upon the vascular anatomy and harvested on the non-radiated side when possible. Complications and functional outcomes were assessed. Results: All flaps (n=8) were harvested under 1 hour, and patients had uneventful post-operative recovery. All ablative wounds and donor sites were closed primarily and did not require additional surgery. One patient, after undergoing a hemi-phyangegalic reconstruction with a normal swallowing study 1 week post-operatively, developed a small controlled leak that subsequently resolved. This patient had received pre-operative radiation. Another radiated patient, after undergoing mandibular fibular free flap and soft tissue reconstruction, developed distal supraclavicular flap necrosis secondary to tight skin closure over the flap. None of the patients demonstrated had functional donor site morbidity. One patient noted referred sensation to the shoulder in the immediate post-operative period. Conclusions: This is the first reported series describing the use of a pedicled supraclavicular artery flap for head and neck oncologic reconstructions that would have otherwise required a regional or free flap. The supraclavicular artery flap is an excellent flap option for poor microvascular surgical candidates or patients who do not wish to have a free tissue transfer. This thin flap is easy and quick to harvest, has a reliable pedicle, and has minimal donor site morbidity.

Table I: Common Head and Neck Reconstruction Flaps

<table>
<thead>
<tr>
<th>Flap Choice</th>
<th>Regional/Free</th>
<th>Flap Type</th>
<th>Thin/Bulky</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectoralis Major</td>
<td>Regional</td>
<td>Musculocutaneous</td>
<td>Bulky</td>
</tr>
<tr>
<td>Deltopectoral</td>
<td>Regional</td>
<td>Musculocutaneous</td>
<td>Bulky</td>
</tr>
<tr>
<td>Trapezius</td>
<td>Regional</td>
<td>Musculocutaneous</td>
<td>Bulky</td>
</tr>
<tr>
<td>Forearm</td>
<td>Free</td>
<td>Fasciocutaneous</td>
<td>Thin</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>Free</td>
<td>Fasciocutaneous</td>
<td>Thin/Bulky</td>
</tr>
<tr>
<td>Parascapular</td>
<td>Free</td>
<td>Fasciocutaneous</td>
<td>Thin/Bulky</td>
</tr>
<tr>
<td>Superficial Epigastric</td>
<td>Free</td>
<td>Fasciocutaneous</td>
<td>Thin/Bulky</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>Regional</td>
<td>Fasciocutaneous</td>
<td>Thin</td>
</tr>
</tbody>
</table>

S189: DESIGNING CHIMERA FLAPS IN MULTIPLE VASCULAR SYSTEMS

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**Medical Oncology/Concurrent Therapies**

**S190: BIOMAB EGFRTM (NIMOTUZUMAB/H-R3) IN COMBINATION WITH STANDARD OF CARE IN SQUAMOUS CELL CARCINOMA OF HEAD AND NECK (SCCHN)**

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**Objective:** EGFR is over expressed in most malignant tumors of epithelial origin. BIOMAB EGFRTM, a humanized recombinant anti-EGFR mAb acts specifically as an active inhibitor of EGFR resulting in blockade of growth factor binding receptor activation and subsequent signal transduction events. Preclinical studies demonstrated antiproliferative, antiangiogenic and pro apoptotic activity of hR3. **Materials and Methods:** An open label, multicentric randomized study was conducted in India using BIOMAB EGFRTM in combination with RT and Chemotherapy (CT) and Standard RT alone, in treatment of SCCHN. Subjects with stage III and stage IV SCCHN, suitable for CT + RT and RT alone were randomly assigned to BIOMAB EGFRTM + RT or RT alone and BIOMAB EGFRTM + CT + RT or CT + RT. 80 evaluable subjects were planned to be recruited considering a sample size of 20 per arm. BIOMAB EGFRTM was given at a dose of 200 mg weekly once for 6 weeks. The primary endpoints were Response rates and Safety. RECIST was used for Tumor evaluation. Adverse events were classified according to toxicity grades [CT-CTC AE (version 3) and RT, [RTOG]]. **Results:** 76 subjects were evaluable at 24 weeks post treatment. 17 in BIOMAB EGFRTM + RT arm, 19 in RT arm, 20 in BIOMAB EGFRTM + CT+RT and 20 in CT+RT arm. BIOMAB EGFRTM related toxicity was limited to expected and reversible grade 1 & 2 toxicity. Of these, only chills and rashes were rated as certainly related to BIOMAB EGFRTM. An objective response rate of 76% was achieved in BIOMAB EGFRTM + RT arm, 40% in RT arm (p = 0.023): 100% in BIOMAB EGFRTM + CT+RT arm and 70% in CT + RT arm (p = 0.020). The Overall Survival % at 15 months was 64.7% in BIOMAB EGFRTM + RT arm, 57.9% in RT arm, 95% in BIOMAB EGFRTM +CT+RT arm and 70% in CT + RT arm. **Conclusion:** BIOMAB EGFRTM has a favourable safety profile and addition of this drug to standard of care in SCCHN can help to achieve better tumor responses and also increase survival without potentiating toxicity.

**S191: SEQUENTIAL THERAPY FOR LOCALLY ADVANCED LARYNX AND HYPOPHARYNX CANCER: ANALYSIS OF SURVIVAL AND FAILURE IN TAX 324**

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**Objective:** To quantitatively overall survival (OS), progression free survival (PFS), and laryngectomy free survival (LFS) in patients with locally advanced larynx and hypopharynx cancer treated in the Phase III TAX 324 trial, a comparison of which compared two induction chemotherapy regimens as part of sequential treatment. **Methods:** Patients with larynx and hypopharynx cancer enrolled in TAX 324 were identified. Treatment consisted of induction with either docetaxel, cisplatin and 5-fluorouracil (TPF) or cisplatin and 5-fluorouracil (PF), both followed by chemoradiotherapy (CRT) with weekly cisplatin and concurrent surgery as necessary to tumor response or persistence. Patients were followed for a minimum of two years and data on demographics and outcomes were extracted from Case Report Forms and analyzed. Details of treatment and overall safety have been reported [NEJM, 2007]. **Results:** Among 501 evaluable patients enrolled in the trial, 89 had larynx and 77 had hypopharynx cancer (n=166). Of these, 90 were randomized to TPF and 76 to PF. There were no significant differences between the TPF and PF patients with regard to age, sex, site of disease, PS, resectability, or nodal stage. With 41 months median follow-up, efficacy results (TPF vs. PF) include median OS 59 (31-119) vs. 24 (13-42) months with Hazard Ratio (HR) 0.62 [0.41-0.94; p=0.024] and 3 year OS 57% [26-68%] vs. 40% [28-52%]. Median PFS is 21 (12-58) vs. 11 (8-14) months with HR 0.66 [0.45-0.97, p = 0.032] and 3 year PFS 43% [32-54%] vs. 29% (19-40%). There were 67 and 56 subjects in the TPF and PF treated groups, respectively. Disease free survival (DFS) was a primary endpoint of the trial, Laryngectomy Free Survival (LFS) among operable subjects was significantly greater with TPF compared to PF, p = 0.03. Primary site surgery was less frequent in the TPF group compared to PF, 10% vs. 20%, respectively, as was neck dissection, 19% vs. 38%, respectively. The proportion of patients requiring surgery was significantly lower in the TPF group (22% vs 42%, p <0.02). **Conclusions:** Among patients with larynx or hypopharynx cancer, induction TPF followed by chemoradiotherapy results in a significant 38% reduction in mortality risk and a significant prolongation of PFS, compared to PF induction. Among operable subjects, there is a decreased need for primary site surgery and a significant improvement in LFS. These results support sequential therapy with TPF as another standard for organ preservation in advanced larynx and hypopharynx cancer. 1. Posner, M. R., Hershock, D. M., Blajman, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med, 357: 1705-1715, 2007.

**S192: CHEMOTHERAPY ALONE FOR COMPLETE RESPONDERS TO INDUCTION CHEMOTHERAPY FOR ORGAN PRESERVATION IN ADVANCED LARYNGEAL CANCER**

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**Objective:** Response to a single course of induction chemotherapy in advanced laryngeal cancer has been successfully used to select primary surgery or chemoradiation as definitive treatment with 87% 3 yr overall survival and a high rate of laryngeal preservation. Intensive chemoradiation is associated with increased toxicities that affect speech and swallowing. Because 15-20% of patients achieve a complete histologic tumor response (HCR) after a single neoadjuvant cycle, we designed a phase II trial to determine if 6 cycles of alternating chemotherapy [cisplatin/5-FU, docetaxel] after HCR was feasible and result in less toxicity and improved voice related QOL compared to chemoradiation. **Methods:** Studied were 32 patients with Stage III (10) or Stage IV (22) laryngeal or hypopharyngeal cancer. Tumor site was glottic in 8, supraglottic in 20 and hypopharynx in 4. 30% were N0, 70% were N+. All patients received 1 cycle of induction cisplatin 100 mg/m2 & 5-FU 1000 mg/m2/day x 5 days (P/5FU). Patients with 100% clinical and histologic response (HCR) received alternating cycles of P/5FU, followed by weekly docetaxel (D) 35 mg/m2 x 3 weeks for 6 cycles. Patients with >50% response (PR) received radiation (CRT) with 70 Gy and concurrent P 100 mg/m2, days 1, 22, & 43. Patients with ≤50% response underwent laryngectomy. Final planned tumor assessment by laryngoscopy and biopsy was performed 8 weeks after CRT or 3 weeks after the last cycle of P/5FU (CT alone arm). Median follow-up was 44 months [range 33-56 months]. **Results:** HCR was achieved in 4 patients (13%), PR in 24 (75%) and <PR in 4; and of these non-responders (NR) 3 had surgery and one refused. Toxicity was acceptable. Or 3/4 granulocytopenia 19%; Gr 3/4 mucositis with CT alone 12.5%. All 4 CT alone patients relapsed in the neck and required subsequent surgery and postoperative CRT because of multiple nodes or extracapsular spread. Because this rate of salvage XRT met our trial stopping rules, patient accrual was closed at 32 patients. Of the CT alone patients, 1 is alive without disease, 1 died of complications, and 2 died from disease. A total of 6/24 who received CRT failed; 3 had surgery; and 3 were unresectable. None of the NRs received only one has died (leukemia). Overall survival at 5 yrs was 68% at 3 yrs. [95% CI = 52.7%, 84.8%]. Three year DFS is 62.5% [95% CI = 45.7%, 79.3%]. Only 2 patients developed distant metastases. Successful larynx preservation was achieved in 25 patients (78%). **Conclusions:** Our findings indicate that CT alone is not feasible for long term control of regional disease in advanced laryngeal cancer. HCR patients may represent a subpopulation for testing other innovative approaches that reduce long term toxicity. Overall survival and larynx preservation rates were excellent and similar to our prior experience. Planned integration of early regional control by surgery may be necessary to allow CT only treatment approaches that spare patients radical RT.

**S193: RECENT RESULTS OF TREATMENT OF BASE OF TONGUE EPIDERMOID CARCINOMA WITH CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY**

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**Objective:** To determine the response to a new concurrent chemotherapy and radiation regimen for patients with epidermoid carcinoma of the base of tongue. The regimen consists of cisplatin and fluorouracil concurrently with radiation therapy. **Methods:** Out of 101 patients treated at this institution from 1993 to 2000, 40 patients qualified for this study. Tissue diagnosis was confirmed by the University of Massachusetts Cancer Center 1993-2000. All patients were treated with cisplatin 100 mg/m2 and fluorouracil 1000 mg/m2 for 5 days with concurrent radiation therapy involving 70 Gy. **Results:** The median follow-up of all patients is 41 months. Of the 40 patients treated with concurrent cisplatin and fluorouracil and radiation therapy, 33 patients (83%) are still alive with no evidence of disease. **Conclusions:** The combination of cisplatin and fluorouracil provides a good therapeutic ratio for stage IV disease. This regimen is well tolerated with minimal treatment-related toxicity.
One hundred patients were treated with CR + RT. Over the last decade chemotherapy and radiotherapy have become established standard treatments for treating patients with advanced stage squamous cell carcinoma of the head and neck. From 1996 to 2007, 92 previously untreated patients with squamous cell carcinoma of the head and neck base were treated at our Institution. There were 80 men and 12 women with an average age of 59 years. Twenty-four patients (26%) had no history of tobacco use. Twenty-seven were remote former smokers and 41 (45%) were current smokers. HPV infection appeared to be an etiologic factor in the non-smokers. Twelve patients presented with stage I or II disease. The remaining 80 had stage III or IV disease. Fifty-three patients were treated with initial concurrent chemoradiotherapy and radiotherapy (CTX+RT). Nineteen patients were treated with radiotherapy as primary treatment and 12 were treated with initial surgery. Eight patients were treated with palliative intent or lost to follow-up. Twenty-four patients undergoing initial non-surgical therapy were treated with subsequent surgery (usually neck dissection alone) for persistent or suspected persistent disease. Sixty-one patients underwent gastrostomy tube placement as part of their treatment. Median follow-up time was 4 years with a range from 1 month to 11 years. Results: For patients treated with CTX+RT, the complete response rate at the primary site was 85% and 72% in the neck. Overall, 70% of patients were disease free at last follow-up. There were no significant difference in survival between the treatment groups (CTX+RT, primary radiotherapy and primary surgery) with those remaining disease free, 70%, 74%, and 67%, respectively. Former and non-smokers tended to fair better than smokers (76% vs. 63% disease free) but this difference was not statistically significant. For patients undergoing CTX+RT, failure to achieve a complete response at the primary site carried a very poor prognosis. Only one of eight patients in this category has survived. There were six treatment related deaths (6%) in this series. Two deaths were post-operative following salvage surgery for persistent disease following CTX+RT. Four deaths occurred as a result of septic complications following CTX+RT. For patients treated with CTX+RT, hospitalization was required during treatment in 21%. Twenty-six percent of patients in this group developed severe dysphagia. Conclusions: CTX+RT has a high response and cure rate for advanced stage squamous cell carcinoma of the tongue base. The survival rates are similar to other modalities. There is a relatively high complication rate associated with CTX+RT. However, it is accepted that the morbidity of CTX+RT is less than those associated with tongue base resection.

S194: WEEKLY PLATINUM-BASED CHEMOTHERAPY WITH CONCURRENT RADIOTHERAPY (CRT) FOR LOCALLY ADVANCED HEAD/NECK CANCER (LAHNC) J.M.Watkins1, A.E.Herrin1, K.S.Shrin1, E.Garrett-Mayer1, R.K.Stuart1, M.B.Gillespie1, T.A.Day1, A.K.Sharabi1, 1Medical University of South Carolina, Charleston, SC

Objective: LAHNC are optimally treated with either definitive CRT or resection followed by radiotherapy +/- chemotherapy. The optimal CRT regimen remains to be identified; the present study analyzes long-term outcomes of a regimen employing weekly low-dose platinum-based chemotherapy and concurrent daily radiotherapy. Methods: Patient, tumor, treatment, toxicity, and outcome data were collected and entered into a clinical database. Included patients had resectable or unresectable LAHNC (oral cavity, oropharynx, larynx, hypopharynx) treated with curative-intent CRT using weekly platinum-based chemotherapy with concurrent radiotherapy. Pre-CRT neck dissection is common but permitted provided primary site was clinically detected and unadressed. All treatment was conducted at a single institution, and patients with post-CRT follow-up <6 months were excluded (unless recurrence or death). Loco-regional control, freedom from failure, disease-specific survival, and overall survival were analyzed using Kaplan-Meier estimation. Disease control and survival intervals were measured from date of CRT initiation to appropriate endpoint (loco-regional failure, any second malignancy, cancer-specific mortality, and any mortality, respectively). Results: One hundred patients were treated with CRT using weekly platinum-based chemotherapy, of whom 96 were eligible for present analysis (4 excluded for insufficient follow-up). Median age was 59 years (range 43-92), 83% were male and 68% were white. The most common primary sites were: oropharynx (62%), larynx (20%), and hypopharynx (12%) (12 patients had a synchronous III/VB disease and stage II). The primary site was staged as unresectable (cT4b) in 9 patients (9.4%). Six patients underwent pre-treatment neck dissection. Radiotherapy was prescribed to a median of 70 Gy (range 66-80) to gross disease, 54% were planned and treated using a simultaneous integrated boost intensity-modulated radiotherapy technique. Chemotherapy regimens employed were as follows: cisplatin/paclitaxel (88%); 20/30 mg/m²/wk, carboplatin (AUC 2/wk) and paclitaxel (8%), and carboplatin only (4%). CRT was well-tolerated; 96% of patients completed >/=66 Gy RT and 86% completed >/=6 cycles of intended chemotherapy. At median survivor post-CRT follow-up of 46 months (range 1-165), 47% of patients are alive without evidence of disease. Estimated loco-regional control rates at 2 and 4 years were 70.5% (CI 60.9%-81.5%) and 61.6% (50.5%-75.1%), respectively. Estimated 2- and 4-year freedom from failure rates were 60.6% (51.0%-72.1%) and 48.0% (37.4%-61.5%), respectively. Estimated 2- and 4-year disease-specific survivals were 76.1% (67.4%-85.9%) and 74.5% (65.5%-84.7%), respectively. Estimated 2- and 4-year overall survivals were 68.8% (59.9%-79.8%) and 47.8% (43.9%-68.5%), respectively. Median time to recurrence was 5.9 months (range 0-60), with 85% occurring within 24 months post-CRT. Initial sites of recurrence were loco-regional (22 patients), distant (14), and loco-regional + distant (5). Conclusions: Weekly low-dose platinum-based chemotherapy with concurrent radiotherapy is tolerable and efficacious as definitive CRT for LAHNC. Loco-regional control, freedom from failure, disease-free survival, and overall survival are comparable with standard CRT regimens, and do not appear to have an adverse effect on the frequency, timing, or pattern of disease recurrence.

S195: FOLLOW UP FOR HEAD AND NECK CANCER PATIENTS WITH N 2-3 ACHIEVING A COMPLETE RESPONSE AFTER CHEMOTHERAPY + RADIOTHERAPY L.Califano1, E.E.Giglia1, P.Saco1, A.Gonzalez1, R.Adam1, G.Urrutia1, A.Voogd1, J.Acogliani1, C.Rufino1, R.Pradier1, 1Instituto Angel H. Roffo, Buenos Aires, Argentina

Background: The N Status is a major prognostic factor for recurrence in patients with head and neck cancer. The management after complete response of N greater than 3 cm is still controversial. There are no randomized trials that address the issue if a prophylactic neck dissection should be performed after complete response for N2-3 disease. Objectives: To analyze the rate of recurrence in the neck considering the pretreatment N size in patients with a complete response after simultaneous chemotherapy and radiotherapy (CT+RT) in order to establish a guide in our institution to select the ones that would benefit with an elective neck dissection. Material and Methods: The records of 198 patients with squamous cell carcinoma of the head and neck treated with CR+RT were analyzed. 185 pts were male (93, 43%), median age: 58 years. Tumors sites: larynx: 115 pts, oropharynx: 58 pts, oral cavity: 13 pts, paranasal sinus: 7 pts, hypopharynx: 3 pts. HPV infection appeared to be an etiologic factor in the non-smokers. There was no significant difference in survival between the three treatment groups (CT+RT, primary radiotherapy and primary surgery) with those remaining disease free, 70%, 74%, and 67%, respectively. Former and non-smokers tended to fair better than smokers (76% vs. 63% disease free) but this difference was not statistically significant. For patients undergoing CTX+RT, failure to achieve a complete response at the primary site carried a very poor prognosis. Only one of eight patients in this category has survived. There were six treatment related deaths (6%) in this series. Two deaths were post-operative following salvage surgery for persistent disease following CTX+RT. Four deaths occurred as a result of septic complications following CTX+RT. For patients treated with CTX+RT, hospitalization was required during treatment in 21%. Twenty-six percent of patients in this group developed severe dysphagia. Conclusions: CTX+RT has a high response and cure rate for advanced stage squamous cell carcinoma of the tongue base. The survival rates are similar to other modalities. There is a relatively high complication rate associated with CTX+RT. However, it is accepted that the morbidity of CTX+RT is less than those associated with tongue base resection.

S196: ORGAN PRESERVATION WITH CONCURRENT CHEMORADIATION FOR ADVANCED LARYNGEAL CANCER: ARE WE SUCCEEDING? L.Lambert1, B.Fortin1, D.Soulieres1, L.Guerin1, G.Coulombe1, D.Charpentier1, J.C.Tabet1, M.Belair1, L.Ligibashian1, P.F.Nguyen-Tan1, 1Centre Hospitalier de l’Universite de Montreal (CHUM), Montreal, PQ, Canada

Objectives: To determine the rates of organ preservation and function in patients with advanced laryngeal and hypopharyngeal carcinomas treated with concurrent chemoradiotherapy (CRT). Methods: Between April 1999 and September 2005, 82 patients with advanced laryngeal (67%) and hypopharyngeal carcinomas (33%) underwent conventional radiotherapy and concurrent platinum-based chemotherapy with curative intent. Sixty-two patients were male (75.6%) and 20 female (24.4%) with a median age of 59 years. 22% of patients were stage III and 78% were stage IV. The intended dose was 70 Gy in 2 Gy fractions or 72Gy in 1.8 Gy fractions (4.8%). Nine patients did not receive the prescribed dose of radiotherapy. Median follow-up was 3.8 years. Results: Overall survival and disease-free survival were respectively 63% and 73% at 5 years.

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response from CRT was 75%. 19 patients (23%) experienced significant complications following CRT: 6 (7.3%) required a percutaneous gastrostomy, 5 (6%) had persistent grade 2 and 3 dysphagia, 2 (2.4%) had pharyngo-oesophageal stenosis requiring multiple dilatations, 2 (2.4%) had chronic lung aspiration and 7 (8.5%) required a permanent tracheostomy. 4 patients (4.9%) underwent laryngectomy without pathological evidence of disease. At last follow-up, 5 (6%) patients were still dependent on gastrostomy. Overall, 42 (52%) patients with complete response and had a functional larynx with no other major complications. Conclusions: Half of all patients in the study with advanced laryngeal or hypopharyngeal carcinomas, treated with CRT, either experienced significant complications of laryngeal failure or locoregional relapse. Percutaneous gastrostomy dependency and laryngectomy are negative outcomes for patients treated with an objective of preservation of a functional larynx. More effort and studies are necessary to further improve locoregional control, quality of life and reduce late complications.

S197: THE USE OF CONCURRENT CHEMORADIATION IN THE TREATMENT OF ADVANCED T4 LARYNGEAL CANCER
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Objectives: The current mainstay of treatment for advanced T4 laryngeal cancers is total laryngectomy with adjuvant therapy. The objective of this study is to evaluate the survival outcome at our institution following concurrent chemoradiation as the initial definitive treatment in a series of patients diagnosed with advanced stage (T4) glottic and supraglottic squamous cell carcinomas. Additionally, we aim to determine secondary clinical outcomes following chemoradiation, with regard to locoregional control, laryngeal preservation, and late complications.

Methods: Following IRB approval, we retrospectively reviewed the experience at our institution from January 1998 to December 2006 of all patients diagnosed with advanced stage (T4) glottic and supraglottic squamous cell carcinomas treated with concurrent chemoradiation as the definitive treatment modality. Seventeen patients (12 male/5 female) were included in this study with a mean age of 59 years (range 44-72 years). At the initiation of treatment, 6 patients (35%) had evidence of thyroid cartilage invasion. The chemotherapy protocol utilized in the majority of patients (71%) consisted of two cycles of Cisplatin and 5-Fluorouracil while the remaining patients (29%) who were deemed medically unfit to tolerate this regimen received alternative agents. All patients completed standard fractionation radiotherapy at a minimum of 70 Gy. Overall patient survival was analyzed utilizing a Kaplan-Meier method. Results: In this cohort of patients, the overall survival probability at 2 years and at 5 years was 64% and 53%, respectively. Nine patients in this series ultimately died at a mean of 32.4 months (range 3.0-74.3 months) after treatment while the remaining 8 patients have a mean follow-up of 44.0 months (range 1.0-74.2 months). Laryngeal preservation was maintained in 88% of patients. Secondary complications included 29% of patients requiring esophageal dilation for dysphagia and 2 patients (12%) underwent a salvage laryngectomy both of which belonged to the subset of patients with extensive thyroid cartilage invasion. However, no patients were percutaneous gastrostomy (PEG) tube dependent. Conclusion: The results of our study indicate that concurrent chemoradiation therapy is a satisfactory treatment regimen for patients with advanced stage (T4) glottic and supraglottic squamous cell carcinoma even with cartilage invasion. Laryngeal preservation was maintained in 88% of patients. Secondary complications included 29% of patients requiring esophageal dilation for dysphagia and 29% of patients requiring a permanent tracheostomy. No patients were PEG tube dependent.

S198: CONCURRENT CHEMORADIOThERAPY AND GEFITINIB FOR LOCOREGIONALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CANCER (HNSCC)
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Objectives: Concurrent chemotheraphy and radiation has improved locoregional control and survival in locoregionally advanced HNSCC. Distinct metastases have now emerged as a more frequent cause of treatment failure. This phase II clinical trial explored whether long term maintenance gefitinib, an oral epidermal growth factor inhibitor, would reduce distant metastases and improve overall survival when added to our previously tested multi-agent concurrent chemoradiotherapy regimen. Methods: Patients with previously untreated Stage III/IV (MO) HNSCC were treated with hyper-fractonated radiation (72-74.4 Gy at 1.2 Gy bid) and two courses of concurrent chemotherapy using fluorouracil, 1000 mg/m2/day and cisplatin, 20 mg/m2/day; both given as 96 hour continuous intravenous infusions during weeks 1 and 4 of the radiation. Gefitinib, 250 mg daily was begun on the first day of radiation and was to be continued for a total of 2 years. Primary site resection was reserved for residual or recurrent primary site disease after chemoradiotherapy. Neck dissection was considered for N2 or greater disease, irrespective of clinical response, and for residual or recurrent neck disease after chemoradiotherapy. Results from this trial were repetitively compared to our previous study which tested an identical chemoradiotherapy regimen without gefitinib maintenance. Results: Between 4/03 - 9/07, 60 patients were enrolled on this trial. Demographics and disease extent were statistically similar to our historical experience; 53 patients (88%) were male, 58 (97%) were Caucasian, and the median age was 58 (range 24-75) years. Primary sites included oropharynx in 41 patients (68%), larynx in 12 (20%), hypopharynx in 7 (11%) and oral cavity in 5 (8%). There were 48 Stage IV patients (80%) and 29 (48%) with T4 tumours. Toxicities were similar to our historical experience and included grade 1-4 mucositis/dysphagia in 92%, and infield dermatitis in 30%. Neutropenia<1000/mm3 occurred in 77%, requiring re-hospitalization for neutropenic fever in 63%. However, transient renal dysfunction was worse in patients receiving gefitinib (28% vs. 5%, p=0.002), as was all-cause re-hospitalization (83% vs. 64%, p=0.02). Gefitinib-specific toxicity included grade 1 skin reaction in 36 patients (60%) and diarrhea in 21 (35%). There were 5 early deaths on the gefitinib-containing trial due to aspiration pneumonia (2) ischemic bowel (1), pneumonia embolism (1) and sudden death (1). With a median follow-up of 25 months, 2-year projected Kaplan-Meier outcomes were not statistically different between the gefitinib- and non-gefitinib-containing trials, including overall survival (82% vs. 80%), freedom from recurrence (74% vs. 74%), local control without surgery (82% vs. 88%), and distant metastatic control (86% vs. 81%) respectively. Patient tolerance of gefitinib proved difficult. Only a projected 46% of patients will complete the scheduled 2 years of gefitinib maintenance. Patients taking the medication, however, took a median of 94% (range 47-100%) of their prescribed pills. Conclusions: In this study of patients with locoregionally advanced HNSCC, the addition of this dose of gefitinib to our multi-agent concurrent chemoradiotherapy regimen was not well tolerated. When compared to our historical experience it appeared to produce additional toxicity, with no improvement in any measured outcome.

ROBOTICS AND INNOVATIVE TECHNOLOGIES

S199: TRANSORAL ROBOTIC SURGICAL EXTRICATION OF OROPHARYNGEAL NEOPLASMS
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Background: Transoral robotic surgery allows the surgeon to perform typical surgical maneuvers in a limited space with increased dexterity and visualization. We describe our surgical experience with 35 patients enrolled in a prospective phase 1 clinical trial for removal of oropharyngeal squamous cell carcinoma. The feasibility, morbidity, immediate outcomes and functional results are reported. Results: Thirty five patients with oropharyngeal squamous cell carcinoma were enrolled in a prospective phase 1 clinical trial for surgical removal with the DaVinci surgical robot. All patients successfully underwent complete surgical removal with negative intraoperative frozen section margins. All patients were discharged from the hospital within six days and all patients returned to oral diet and were decannulated from their tracheostomy tube within two weeks of the procedure. There were no oral cutaneous fistulas and no patients developed postoperative bleeding or infection. Conclusion: Transoral robotic surgery offers the surgeon the ability to resect oropharyngeal squamous cell carcinoma with effective visualization of the tumor and adequate exposure for complete tumor removal in selected cases. The morbidity of this procedure is acceptable and immediate postoperative functional results suggest that airway control and return to swallowing are improved over traditional open approaches. Future data will report on long-term oncologic and functional outcomes.

S200: TRANS ORAL ROBOTIC SURGERY: INDICATIONS AND LIMITATIONS FOR MANAGEMENT OF LESIONS OF THE UPPER AERODIGESTIVE TRACT
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Objective: To assess the indications and limitations associated with TORS in an effort to determine the optimal application of the robot for head and neck surgery. Methods: A retrospective review was conducted of patients who underwent TORS for the management of benign and malignant disease. Patient-specific factors were evaluated including tumor site, tumor stage, patient anatomy, body habitus, body mass index, degree of trismus, and mandibular - mid-face skeleton. Also evaluated were time to set up the robotic arms, retraction techniques, operative time, and operative complications. Results: Thirty- one patients underwent TORS for the management of benign and malignant disease. Twenty- six procedures were successfully completed while five procedures were terminated for a variety of reasons, and six procedures were completed but represented difficult cases as a result of limitations of the robot. Of the thirty- one procedures that were attempted, the primary lesions were located at the following sites: Palate (6), tonsil (12), hypopharynx (4), larynx (6), parapharyngeal space (2), and esophageal inlet (1). Pathological diagnoses included squamous cell carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, vascular malformation, cricopharyngeal stricture, and velopharyngeal insufficiency. Evaluation of the five terminated procedures demonstrated that in all cases, failure was related to restricted access to the lesion. The restricted access was a result of a retromolar mandible (2), the inability to effectively retract the peripheral soft tissue (1), and the inability to access the lesion because of bulky nature of the robotic arms (2). Failures occurred in the following anatomic sites, esophageal inlet (1), larynx (2), and base of tongue (2). Tumor site, tumor stage, body habitus, body mass index, and mid-face skeleton were not related to surgical technique failure. Evaluation of all failure cases demonstrated that in all cases, the bulky nature of the robotic arms resulted in restricted movement of the robotic arms. While the cases were completed, access and movement was restricted. Conclusion: TORS offers a potentially minimally invasive approach for the management of select head and neck pathology. In this limited experience, a hypoplastic mandible and lesions at the level of the glottic larynx and esophageal inlet represent a challenge to access as a result of the current instruments available for retraction and the bulky nature of the robotic arms. The inability to draw the robotic arms into a more linear vector also represents a limitation to access and movement. Methods to improve the angle of instrument insertion into the oral cavity and soft tissue retraction would improve the application of the robot to head and neck surgery.

S201: TRANSPORTAL ANATOMY IN THE CONTEXT OF TRANSORTAL ROBOTIC SURGERY (TORS): A CADaver STUDY

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Objective: Traditional treatment for carcinomas of the aerodigestive tract has included open surgical approaches. These open approaches have the advantage of allowing for control of critical neurovascular structures under direct visual control. In an effort to decrease morbidity associated with open surgery, we have used the new technique of Transoral Robotic Surgery (TORS) for treatment of selected carcinomas of the oropharynx, hypopharynx, and larynx. While TORS has many advantages including decreased morbidity and improved magnification, this technique does not allow direct vascular control. Furthermore, this technique approaches key anatomic landmarks from inside-out, in a way that may be unfamiliar to many surgeons. In an effort to better define transoral anatomy, we performed a cadaver study to define the precise locations of key neurovascular landmarks encountered during TORS. Methods: We obtained 6 fresh, frozen human cadaver heads for this study. The cadaver heads were then dissected to allow access for the dissection. The sites most frequently addressed during TORS were dissected, including the tonsil, tongue base, supraglottic larynx, and hypopharynx. At each site, we began the dissection transectionally and dissected out the deeper structures. We took measurements from anatomic landmarks to each of the key neurovascular structures encountered at each site. Once the dissection was completed transectionally, it was repeated transorally, and measurements were again taken. Results: For each site, we took measurements from identifiable landmarks to the key arteries and nerves encountered. At the tongue base, we measured the distance from the mucosa of the midline and lateral tongue at the level of the circumvallate papillae to the lingual artery, lingual nerve, and hypoglossal nerve. The same measurements were then taken using the retromolar trigone as a stable bony landmark. In the tonsillar fossa, we measured the distance from the anterior tonsillar pillar to the internal carotid artery, branches of the external carotid as well as the glossopharyngeal and vagus nerves. Again, we used the retromolar trigone as a stable bony landmark to make the same measurements. In the larynx, the distance from the aryepiglottic fold to the superior laryngeal neurovascular bundle was measured. In the hypopharynx, we measured the distance from the lateral mucosa, as well as the perifrontal sinus to the internal carotid artery. Conclusions: TORS is a new technique that we have used to treat select carcinomas of the oropharynx, hypopharynx, and larynx. This technique approaches important neurovascular structures in a way that may be unfamiliar to many surgeons. This cadaver study defines the precise location of the important arteries and nerves as they are encountered during TORS. A more thorough knowledge of this anatomy will allow TORS to be performed safely and efficiently for the treatment of carcinomas of the aerodigestive tract.

S202: RECONSTRUCTION OF THE SKULL BASE WITH A TRANSANTRAL ROBOTIC SURGICAL APPROACH

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Objective: Transnasal endoscopic approaches are being increasingly utilized for surgical access and resection of tumors of the anterior and central skull base. One major limitation of this approach is the inability to provide water-tight dural closure and reconstruction. Our objective is to describe the feasibility of a robotic-assisted surgical reconstruction of the anterior and central skull base with a watertight dural closure and reconstruction. Methods: The surgical exposure begins with a bilateral Caldwell-Luc approach. Transantral access to the nasal cavity is gained through bilateral middle meatal antrotomies. A posterior nasal septectomy is performed and the nasal septal mucosa is preserved bilaterally as free mucosal grafts. Robotic-assisted bilateral ethmoidectomies and sphenoethmoidectomies are performed, and the sphenoid plate and portion of the underlying dura is resected. A free mucosal autograft or a fascial graft is then sutured to the free dural edges to repair the defect. Results: Reconstruction of a dural defect was successfully performed using robotic technique via a transnasal approach. Utilizing both running and interrupted suture techniques, a watertight dural repair was achieved. The most significant advantage of the robotic approach was the ability of the surgeon to perform a two-handed transantral reconstruction of the dura. Conclusions: Transantral robotic surgery provides adequate endoscopic access to the anterior and central skull base. We extend our previous reports and describe the transnasal repair of large dural defects with mucosal or fascial grafts to provide a watertight, tension-free sutured reconstruction. These advantages may expand the indications of minimally invasive endoscopic approaches to the skull base. Further, the feasibility of robotic skull base resections with an acceptable water-tight reconstructive technique is demonstrated.

S203: ENDOSCOPIC ROBOTIC TOTAL LARYNGECTOMY

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Objectives: To develop the technique of endoscopic robotic total laryngectomy. Methods: The technique of endoscopic robotic total laryngectomy was developed in a cadaver lab using an approved protocol, this technique was then applied to a patient with recurrent laryngeal carcinoma following radiation therapy. Results: The procedure was successfully carried out in a human cadaver prior to its performance in a patient. The patient had a T1 interarytenoid laryngeal spindle cell carcinoma treated with full dose radiation therapy 16 months prior to his total laryngectomy. His medical history was complicated by a liver transplant and subsequent chronic immunosuppression. He underwent a successful, negative margin, endoscopic robotic total laryngectomy in July of 2007. He underwent primary endoscopic closure of the mucosal defect and was observed for 2 weeks prior to initiating oral feedings. He swallowed well, with no fistula formation, and was discharged home shortly thereafter. He received a secondary tracheoesophageal pouch, with successful prosthesis placement and vocal rehabilitation, and remains without evidence of disease. Conclusions: Endoscopic robotic total laryngectomy with primary mucosal closure is a feasible and safe procedure. The potential benefits of this procedure include a reduced, or eliminated, fistula risk in salvage total laryngectomy, decreased need for tissue transfer to the site, improved swallowing function with a decreased risk of stenosis, the potential to allow secondary healing instead of mucosal closure and decreased perioperative morbidity.

S204: ROBOTIC NASOPHARYNGECTOMY - A FEASIBILITY STUDY ON A CADAVER MODEL

H.Tay1, D.S.Seeth1, K.Soo2

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Objective: To assess the feasibility and safety of performing robotic assisted resections of head and neck tumors. Methods: Twenty-three patients with oral cavity, oropharyngeal, hypopharyngeal, or laryngeal tumors were identified as candidates for robotic assisted resection utilizing the Da Vinci surgical robot. Operative data collected included robot set up time, adequacy of exposure, ability to perform robotic resection, robotic operative time, blood loss, intraoperative complications, and ability to obtain negative margins. Postoperative data collected included length of hospital stay, date oral nutrition started, diet at discharge, and postoperative complications. Results: In the entire group of 23 patients, 21 patients were considered to have tumors too large for robotic assisted resection at the time of the operation. There were no facial or oral trauma or other intraoperative complications related to the use of the surgical robot. Blood loss was less than 200mL for all resections. Negative margins were obtained in all patients in whom resection was attempted. Sixteen of 17 patients were extubated prior to leaving the operating room. Adequate hemostasis was obtained in all 17 patients. Seventeen (73.9%) patients underwent successful robot assisted resection of their tumors. Four patients had inadequate exposure and 2 patients were considered to have tumors too large for robotic assisted resection. Conclusions: The preliminary results of this series suggest that robotic surgery is technically feasible for the resection of selected oral cavity, oropharyngeal, hypopharyngeal, and laryngeal tumors providing a safe, minimaly invasive alternative to open approaches or primary chemoradiation.

5206: FEASIBILITY AND SAFETY OF ROBOTIC SURGERY FOR UPPER AERO Digestive TRACT NEOPLASMS B.A. Boudreaux1, E.L. Rosenthal1, S.P. Magnuson2, L.K. Clemons3, J.R. Newman2, W.R. Carroll1,1 University of Alabama, Birmingham, AL

Objective: To assess the feasibility and safety of performing robotic assisted resections of head and neck tumors. Methods: Twenty-three patients with oral cavity, oropharyngeal, hypopharyngeal, or laryngeal tumors were identified as candidates for robotic assisted resection utilizing the Da Vinci surgical robot. Operative data collected included robot set up time, adequacy of exposure, ability to perform robotic resection, robotic operative time, blood loss, intraoperative complications, and ability to obtain negative margins. Postoperative data collected included length of hospital stay, date oral nutrition started, diet at discharge, and postoperative complications. Results: In the entire group of 23 patients, 21 patients were considered to have tumors too large for robotic assisted resection at the time of the operation. There were no facial or oral trauma or other intraoperative complications related to the use of the surgical robot. Blood loss was less than 200mL for all resections. Negative margins were obtained in all patients in whom resection was attempted. Sixteen of 17 patients were extubated prior to leaving the operating room. Adequate hemostasis was obtained in all 17 patients. Seventeen (73.9%) patients underwent successful robot assisted resection of their tumors. Four patients had inadequate exposure and 2 patients were considered to have tumors too large for robotic assisted resection. Conclusions: The preliminary results of this series suggest that robotic surgery is technically feasible for the resection of selected oral cavity, oropharyngeal, hypopharyngeal, and laryngeal tumors providing a safe, minimaly invasive alternative to open approaches or primary chemoradiation.

S205: A PILOT STUDY ASSESSING SURGICAL EXPOSURE DURING TRANSORAL ROBOTIC SURGERY (TORS) USING THE DA VINCI ROBOTIC SYSTEM G.S. Weinstein1, B.W.O'Malley1,1 The University of Pennsylvania, Philadelphia, PA

Objective: The primary objective was to assess if the da Vinci® Robotic Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) allows for "adequate exposure" for transoral robotic surgery (TORS). Methods: A human subject protocol was designed and approved by the Hospital of the University of Pennsylvania (Philadelphia, PA) institutional review board. After we obtained written informed consent from them, 128 adult volunteers were included in this prospective study. Inclusion criteria for the TORS protocol consisted of: (1) patients >= 18 at time of treatment, (2) patients must present with indications for diagnostic or therapeutic approaches for benign and malignant diseases of the oral cavity or laryngopharynx, and (3) patients must sign a written informed consent. The primary endpoint of the study was whether "adequate exposure" of the site of the surgical procedure could be obtained to perform the diagnostic or therapeutic transoral robotic surgical procedure. Secondary endpoints included (1) performance of a separate preoperative endoscopy to assess the adequacy of exposure for TORS, (2) an assessment of which mouth gag(s) were during TORS (3) an evaluation of which site were the most common on which to perform TORS and (4) an assessment of the additional time needed to achieve exposure in TORS compared to standard transoral procedures. Results: All TORS cases were performed between May 2005 and June 2007 by the first two authors. Of the 128 patients giving informed consent, 7 ultimately declined surgery in favor of other treatment modalities, 13 agreed to transoral robotic diagnostic evaluation of suspected lesions while the remaining 108 patients were s scheduled for tumor resection via transoral robotic surgery (TORS) using the da Vinci System. Initial clinical and endoscopic evaluation of the mouth, larynx and oropharynx also shows that oropharyngeal lesions were most common (n=82, 76%), followed by lesions of the larynx (n=14, 13.1%), oral cavity (n=8, 7.7%) and hypopharynx (n=4, 4%). TORS could not be performed in 2 patients because of inadequate exposure. Among the 108 patients who underwent therapeutic TORS, 45 patients underwent a separate preoperative endoscopy to assess adequacy of exposure for TORS and the remainder of patients were assessed in the outpatient clinic setting. The Davis-Crow mouth gag (Bausch and Lomb/Stora) was utilized in 47 cases, the FK laryngopharyngoscope (Cyrus) was utilized in 39 cases, the Robotic Atrial Retractor arm was utilized in 3 cases, and the remainder of cases were performed with a variety of mouth gags and retractors with the exception of one case which was performed with no mouthgag or retractor. The additional setup time needed to achieve exposure and robotic positioning for TORS was an addi-

4 minutes when compared to exposure time for standard transoral resection. Conclusions: The most common site for TORS was the oropharynx and the two most common mouth gags utilized were the Davis Crow mouthgags and FK laryngopharyngoscope. In selected cases preoperative endoscopy was found useful prior to the definitive TORS procedure to assess for adequacy of exposure. The setup-time added by the use of the robot was acceptable.

5207: FUNCTIONAL OUTCOMES FOLLOWING TRANS ORAL ROBOTIC PHARYNGOPLASTY FOR MANAGEMENT OF POSTABLATIVE AND PRE EXISTING PHARYN S.D.Selasi1, C.Sung2, T.Kotz1, E.M. Genden2, 1Mount Sinai School of Medicine, New York, NY; 2Mount Sinai School of Medicine, New York, NY

Objective: To evaluate the functional outcomes related to swallowing and speech in a cohort of patients that underwent transoral robotic pharyngoplasty. Methods: Prospectively, speech, swallowing, and quality of life assessments were performed on nine patients who had undergone transoral robotic pharyngoplasty. Modified barium swallow (MBS) was performed to assess nasopharyngeal insufficiency, speech was assessed using the Performance Status Scale for Head and Neck Cancer Patients (PSS) and the Functional Oral Intake Scale (FOIS). Results: Nine patients underwent transoral robotic pharyngoplasty over an eight month period (February 2007 and August 2007). Six patients underwent primary pharyngoplasty immediately following tumor ablation and three patients underwent secondary pharyngoplasty for previously acquired velopharyngeal defects. All nine patients underwent reconstructive pharyngoplasty without intraoperative or postoperative complications. The robot provides excellent visualization and control of the tissue. Postoperatively, all nine patients were able to tolerate an unstructured oral diet. Two patients developed complete nasal obstruction requiring second surgical procedures to reestablish a nasal airway. Postoperative MBS and FOIS demonstrated scores equivalent to normal controls. Conclusions: Transoral robotic pharyngoplasty provides excellent access to the oropharynx for the reconstruction of the velopharyngeal appa-

trons.

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Ethanol exposure resulted in apoptosis in HaCaT cells in a dose
We created a replication-
Cancer stem cells are recently proposed to be the cancer initi-
A non-tumorigenic keratinocyte
Cells infected with Ad5 E6/E7 were able to express mRNA and
Results: Cells infected with Ad5 E6/E7 were able to express mRNA and
Methods: We created a replication-
deficient adenosine virus expressing functional E6/E7. We tested the E6/E7
function of this construct by examining E7 protein levels with p53 and Rb
degradation. Cytotoxic T cell response was assessed in vitro by completing
a time course after vaccination that examined WBC E6/E7 specific gamma
interferon production to control mouse tonsil epithelial cells and mouse tonsil
epithelial cells that express E6/E7. In vivo ability to clear HPV+ tumors was assessed by following tumor growth with or without vaccination.
Results: Cells infected with Ad5 E6/E7 were able to express mRNA and formed functional E6 and E7 proteins. Splenocytes from Ad5 E6/E7 immunized mice only react with cells that express E6/E7 suggesting that mice were able to develop E6/E7-specific immune responses. The time course of gamma interferon response showed that E6/E7-specific gamma interferon production is significantly increased in first two weeks after vaccination and it is substantially maintained at least up to 70 days. To test whether this in vitro finding correlated with tumor clearance C57BL/6 mice were implanted with E6/E7 expressing tumor cells at various times post vaccination. Mice immunized with control adenovirus formed tumors after implantat-
ing E6/E7 MTECs. However, 100 percent of mice immunized with Ad5 E6/E7 cleared E6/E7 MTECs. This ability to clear tumor persisted at least 70 days. Escalating Ad5 E6/E7 doses administered either intra-tracheally or sub-lingually, tumor response was assessed after either orthotopic or subcutaneous implantation of tumor cells. Both delivery methods completely protected mice from forming tumors both at orthotopic sites and distant sites even at relatively low amounts (5X10^5 PFU) of Ad5 E6/E7.
Conclusions: Immunization with adenosine virus expressing functional HPV16 E6 and E7 can be an effective armamentarium for protecting host from E6/E7 expressing HNSCC via generation of potent immune response. This tool may have therapeutic uses to help: 1. augment current vaccine trials that use the HPV L1 therapeutics/tissue engineering

S208: PREVENTING HPV+ HNSCC USING AN ADENOVIRAL VACCINE THAT TARGETS HPV16 VIRAL ONCOPROTEINS

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Objective: Human papillomavirus type 16 (HPV16) is closely associated with head and neck squamous cell cancers (HNSCC), especially in oropharyngeal HNSCC cases. These tumors contain HPV16 E6/E7 oncoproteins which are considered as attractive tumor-specific antigen targets for immunotherapy. In other strategies to induce an antigen specific immune response, replication incompetent adenosine virus has been shown to be a safe and effective method. Thus, we wanted to determine the efficacy of adenosine viral vaccine targeting HPV16 E6/E7 as a therapeutic tool to prevent HPV16 E6/E7 expressing head and neck tumors. Methods: We created a replication-deficient adenosine virus expressing functional E6/E7. We tested the E6/E7 function of this construct by examining E7 protein levels with p53 and Rb degradation. Cytotoxic T cell response was assessed in vitro by completing a time course after vaccination that examined WBC E6/E7 specific gamma interferon production to control mouse tonsil epithelial cells and mouse tonsil epithelial cells that express E6/E7. In vivo ability to clear HPV+ tumors was assessed by following tumor growth with or without vaccination. Results: Cells infected with Ad5 E6/E7 were able to express mRNA and formed functional E6 and E7 proteins. Splenocytes from Ad5 E6/E7 immunized mice only react with cells that express E6/E7 suggesting that mice were able to develop E6/E7-specific immune responses. The time course of gamma interferon response showed that E6/E7-specific gamma interferon production is significantly increased in first two weeks after vaccination and it is substantially maintained at least up to 70 days. To test whether this in vitro finding correlated with tumor clearance C57BL/6 mice were implanted with E6/E7 expressing tumor cells at various times post vaccination. Mice immunized with control adenovirus formed tumors after implantation of E6/E7 MTECs. However, 100 percent of mice immunized with Ad5 E6/E7 cleared E6/E7 MTECs. This ability to clear tumor persisted at least 70 days. Escalating Ad5 E6/E7 doses administered either intra-tracheally or sub-lingually, tumor response was assessed after either orthotopic or subcutaneous implantation of tumor cells. Both delivery methods completely protected mice from forming tumors both at orthotopic sites and distant sites even at relatively low amounts (5X10^5 PFU) of Ad5 E6/E7.
Conclusions: Immunization with adenosine virus expressing functional HPV16 E6 and E7 can be an effective armamentarium for protecting host from E6/E7 expressing HNSCC via generation of potent immune response. This tool may have therapeutic uses to help: 1. augment current vaccine trials that use the HPV L1 capsid protein 2. improve outcomes in combination with current therapies (surgery, radiation, or chemotherapy).

S209: FGFR-RETARGETED ADENOVIRAL GENE THERAPY FOR MRN DISRUPTION INDUCES CISPLATIN CHEMOSENSTIZATION TO HEAD AND NECK CANCER

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Objective of the Study: Cisplatin is one of the most commonly used agents for human head and neck squamous cell cancer (HNSCC). DNA is the critical target for cisplatin induced cytotoxicity. The failure of cisplatin therapy results from development of cisplatin resistance and systemic toxicity occurred by high doses cisplatin. The MRE11/RAD50/NBS1 (MRN) complex is a major DNA repair system and enhanced DNA repair is one of the primary causes for development of resistance in tumor cells to cis-
platin. We have already reported that interruption of the function of MRN by a truncated form of Nbs1 could enhance cisplatin-induced DNA dam-
age and sensitize tumor cells to cisplatin-based chemotherapy for HNSCC at AAO-HNS annual meeting in 2007. Fibroblast growth factor 2 (FGF2) retargeted adenoviral system utilize FGF2 as the targeting ligand and may allow tumor-targeted delivery, improved transduction efficiency, reduced liver toxicity and blocking tumor angiogenesis because of high affinity to FGF, spacial FGF expression in HNSCC and low FGF expression in liver. With that, we hypothesize that FGF2 retargeted mutant Nbs1 aden-oviral gene therapy will enhance the anti-tumor effect of cisplatin for HNSCC through impaired DNA repair and reduced angiogenesis while avoiding systemic toxicity. Methods: Recombinant adenoviral vector expression mutant NBS1 (Ad-NBS1) was constructed. FGF2-Fab’ molecule linked to the adenoviral knob region was conjugated with adenosine (FGF2-Ad). Randomized controlled studies in a murine model with human HNSCC were performed. The established tumors were treated with Ad-NBS1, cisplatin, combined cisplatin and Ad-NBS1, FGF2-Ad-NBS1 or control virus (Ad-DL312). Tumor volume change before and after treatment was measured to evaluate tumor suppression effect. Apoptosis and angiogene-
sis were analyzed to evaluate the mechanism of chemosensitization, and viral localization were examined to assess systemic side effect. Results: Combination of Ad-NBS1 and cisplatin chemotherapy resulted in highly sig-
nificant anti-tumor effects, and combination of FGF2-Ad-NBS1 and cisplatin demonstrated furthermore higher anti-tumor effects. FGF2-Ad-NBS1 with a low dose cisplatin (3mg/kg) demonstrated as same level as combination of Ad-NBS1 and normal dose cisplatin (5mg/kg) when looking at the anti-
tumor effects. Increased apoptosis induction was observed after combina-
tion therapy of cisplatin and both Ad-NBS1 and FGF2-Ad-NBS1. Anti-
angiogenesis effect were observed after combination therapy of cisplatin and FGF2-Ad-NBS1, while combination of cisplatin and Ad-NBS1 group didn’t demonstrate anti-angiogenesis effect. We also confirmed decreasing of viral localization in liver after FGF2-retargeted adenoviral delivery. Conclusion: FGF2 retargeted adenoviral gene therapy for MRN disrup-
tion improves the anti-tumor efficacy by targeting not only DNA repair but also angiogenesis while preventing systemic toxicity by diminishing adi-
oviral localization in the liver. Alteration of viral targeting may provide a novel approach to broaden viral induction, sensitize to chemotherapy and reduce toxicity for the treatment of human HNSCC. The great benefit of this strategy supports further clinical trial.

S210: ETHANOL TRIGGERS APOPTOSIS IN HEAD AND NECK SQUAMOUS CELL CARCINOGENESIS

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Objective: Head and neck squamous cell carcinoma (HNSCC) is character-
ized by field cancerization, which refers to precancerous changes in the mucosal cells of the upper aerodigestive tract that are believed to be the underlying cause of multiple primary tumors. Ethanol, a known risk factor for HNSCC, may have synergistic effects when combined with tobacco car-
cinogens, though the mechanism is poorly understood. We hypothesize that ethanol creates a selective advantage for transformed cells through recurrent apoptosis of normal cells. Methods: A non-tumorigenic keratinocyte cell line (HaCaT) and a tumorigenic keratinocyte cell line (HaCaT II-4) were exposed to increasing concentrations of ethanol, for various durations, and apoptosis was determined with Annexin binding and flow cytometry. In vivo response of oral keratinocytes to ethanol was evaluated by brief exposure of mouse tongues to ethanol and TUNEL staining to detect apoptosis. Results: Ethanol exposure resulted in apoptosis in HaCaT cells in a dose dependent manner. Furthermore, the tumorigenic keratinocyte cell lines were resistant to ethanol-induced apoptosis. TUNEL staining of mouse tongues exposed to ethanol revealed increased apoptosis when compared to untreated controls. Conclusion: Ethanol exposure results in greater apoptosis in normal keratinocytes compared to transformed keratinocytes, thereby conferring a selective growth advantage.

S211: IDENTIFICATION OF STEM-LIKE CELLS IN HEAD AND NECK CANCER CELL LINES

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Objective: Cancer stem cells are recently proposed to be the cancer initi-
ation cells responsible for tumorgenesis and contribute to cancer resis-
tance. Recently several human cancers including leukemia and breast can-
cer and brain tumors were found to contain stem-like cells that play in the development and maintenance of those tumors. Head and neck squamous cell carcinoma is the sixth most common cancer worldwide. High relapse rate and distant metastasis significantly affect 3 years survival rate. We stud-
ied about identifying of stem-like cells in head and neck cancer in vitra in order to develop new treatment strategy targeting the cancer stem cells. Methods: We used two tongue squamous cell carcinoma cell lines, HSC3 and HSC4. Hoechst33342 DNA binding fluorescence dye exclusion, medi-
ated by stem cell surface marker ABCG2 (ATP-binding cassette transporter, G2 subfamily), was assessed by flow cytometry. To test for functional evi-
dence of stem-like cell behavior, we examined HSC3 and HSC4 cells for their ability to form clone. Immunocytochemistry and RTPCR were per-
fomed to detect embryonic stem cell markers, such as Oct3/4, Nanog, and CD133. Results: Although HSC3 showed highly clonogenic ability than HSC4 cells, the clones formed from HSC4 cells exhibited strong posi-
tive staining for endogenous alkaline phosphatases (ALP), which was used as the criterion to identify putative poorly-differentiated embryonic progenitor.
These results suggest that cancer stem-like cells exist in head and neck squamous-cell carcinoma. Existence of SP cells in HSC4 cells appears closely related to high expression of embryonic stem cells markers. Clarifying the key biological markers of stem-cell activity might contribute to the establishment of a novel therapy for head and neck cancer.

S212: NOVEL EPIDEMICAL GROWTH FACTOR RECEPTOR (EGFR) PEPTIDE-SPECIFIC T CELLS FOR COMBINATORIAL THERAPY WITH EGFR-SPECIFIC ANTI

The epidermal growth factor receptor (EGFR) is an attractive target for cancer therapy because it is highly overexpressed and correlated with poor prognosis in epithelial malignancies, including head and neck squamous cell carcinoma (HNSCC). Although clinical responses have been seen using EGFR inhibitors, many individuals do not respond to these treatments. Cetuximab resistant tumor cells cause ubiquitination and degradation of EGFR, increasing its potential as a target for T cell mediated HNSCC lysis. Thus, we propose that T cell based immunotherapy may enhance the anti-tumor efficacy of EGFR targeted therapies. We identified a novel immunogenic wild-type peptide, EGFR(853-861), based on the HLA-A2 binding motif, and modified it to enhance stimulation of anti-EGFR T cells. We found that this peptide induced specific CD8+ T-cell responses in healthy donors after in vitro stimulation. HNSCC cells expressing different levels of EGFR were recognized in a peptide-specific and HLA-A2 restricted fashion. Enhancement of T cell lysis of HNSCC cells was observed after upregulation of tumor antigen processing machinery through IFN-gamma treatment. Combination treatment of HNSCC cells using cetuximab and EGFR(853-861) T cells in vitro shows the feasibility and efficacy of this approach, but this approach must overcome defects in processing and presentation of EGFR peptides in HNSCC cells. Thus, we have identified a novel immunogenic EGFR peptide and used it for preclinical combinatorial therapy with EGFR-specific antibodies. The significance of these results for poor cetuximab responders will be discussed.

S213: THE TOLL-LIKE RECEPTOR 9 AGONIST ODN1826 INHIBITS CACHEXIA AND TUMOR GROWTH IN C26 TUMOR-BEARING MICE

Objectives: Toll-like receptors (TLRs) bind distinct immunogens and activate Nuclear Factor-kB (NF-kB) to regulate innate immunity and inflammatory responses. TLR9 binds viral and bacterial CpG-containing oligodeoxynucleotides (ODNs). TLR9 stimulation inhibits tumor growth in murine models of cancer and synergizes with chemotherapy and radiotherapy to increase tumor cell death. The most highly expressed TLR in skeletal muscle is TLR9, thus TLR9 modulation may have a role in regulating inflammatory responses involved in cancer-related cachexia, a severe muscle wasting condition. Our objectives were to determine whether TLR9 agonists decrease cachexia in tumor-bearing mice and effect tumor growth, and whether TLR9-modulating ODNs would affect activation of Akt and NF-kB pathways in skeletal muscle.

Methods: ODN 2088 is a TLR9 suppressive ODN [Invitrogen, Stcctgagggagtctgagctgcagctg] and ODN 1826 [Invitrogen, Stcctgagggagtctgagctgcagctg] contains a stimulatory CpG sequence. Six-to-eight-week-old male CDF21 mice were divided into four groups: controls, mice injected with the cachexia-inducing C26 murine adenocarcinoma cell line, and mice injected with C26 cells and treated with either ODN 2088 or ODN 1826 (injected subcutaneously with 15 nanomoles/mouse on days 0, 6 and 11). Food intake, mouse weight, and tumor size was measured a.o.d. Immediately after sacrifice tumors and quadriceps were collected and stored at -80°C. Final tumor and hind limb weights were measured. Quadriceps lysates were separated by SDS-PAGE and blotted with mouse-specific antibodies to Akt, NF-kB subunit p65, FoxO1, p70S6K, mTOR and actin (Cell Signaling Technology, MA).

Results: Treatment with TLR9 agonist ODN 1826 afforded a statistically significant increase in final tumor weight (minus final tumor weight) for agonist-treated mice versus tumor-bearing (p = 0.013) and antagonist-treated mice (p = 0.012), although the final weight of the agonist-treated mice was less than that of control mice (p <0.001). Treatment with the agonist also reduced final tumor volume to 845±248 mm3 compared to 1919±1246 mm3 for tumor-bearing mice (p <0.05), while antagonist-treated mice had substantially larger tumors 3132±89 mm3 (p <0.001). Agonist-treated mice also showed greater final hind limb mass than antagonist-treated mice (p <0.001). Western blot analysis of quadriceps muscle showed a statistically significant increase in total p65 for agonist-treated and antagonist-treated mice versus control mice (p =0.03 and 0.02), but not compared to tumor-only mice. There was a significant increase in phospho-Akt for antagonist-treated and agonist-treated mice versus control and tumor-bearing mice (p <0.03, 0.03, and 0.05, and 0.01). Most interestingly, a nearly significant increase in phospho-FoxO1 was found for agonist-treated versus control mice (p = 0.07).

Conclusions: Treatment with TLR9 receptor agonist ODN1826 significantly reduced cachexia caused by the C26 adenocarcinoma tumor in CDF21 mice, with agonist-treated mice having greater final and hind limb weights than tumor-only or antagonist-treated mice. Treatment with agonist ODN1826 increased survival and reduced tumor volume. Treatment with the TLR9 agonist produced a significant increase in total p65 and phospho-Akt in skeletal muscle versus control mice.

S214: NOVEL EPIDEMICAL GROWTH FACTOR RECEPTOR (EGFR) PEPTIDE-SPECIFIC T CELLS FOR COMBINATORIAL THERAPY WITH EGFR-SPECIFIC ANTI

Objective: Treatment of damaged superficial lamina propria of the vocal fold with mesenchymal stem cells from bone marrow has recently shown promise. Adipose derived stem cells (ADSCs) are an alternative source of adult stem cells that may provide a clinical option for rebuilding the damaged superficial lamina propria. We investigated the effects of five biomaterials (hyaluronic acid (HA), collagen, fibrin, co-gel of fibrin and collagen, co-gel of fibrin and HA) on the differentiation of ADSCs, with the long term goal of establishing the conditions necessary for differentiation of stem cells into a functional equivalent of the fibroblasts of the superficial lamina propria.

Methods: ADSCs were isolated from human abdominal adipose tissue using collagen digestion and filtration procedures. The ADSCs were characterized by FACS, immunohistochemistry, and real time PCR. The multipotentiality of ADSCs was tested by using lineage specific media. The ADSCs were cultured in 3D gel scaffold materials for up to 10 days. Gene expression was analyzed by real time PCR and protein expression was studied by immunohistochemistry for stem cell (CD105, CD44) and fibroblast markers (vimentin, prolyl-4-hydrolylase). Results: According to our FACS analysis, over 90% of isolated ADSCs expressed adult stem cell markers. Cells differentiated into osteoblasts and adipocytes according to the differentiation media environment, indicating their multipotentiality. Two fold higher expression of stem cell markers was found in cells grown in HA gel than in cells grown in collagen gel, while collagen and fibrin gels induced two fold higher expression of the decorin and vimentin genes. Cells grown on co-gels of fibrin and HA or fibrin and collagen gels showed elongated morphology and stained positively for vimentin and prolly-4-hydrolylase.

Conclusion: In this study we report that tissue engineering of fibrin co-gel scaffolds with ADSCs enhances expression of fibroblast genes. Our data suggest that tissue engineering of gel scaffolds with ADSCs may provide new understanding of how ADSCs differentiate into vocal fold fibroblasts.

S215: ACUTE VASCULAR DISRUPTION INDUCED BY ASA404 IN AN ORTHOTOPIC MODEL OF HUMAN HEAD AND NECK CANCER

Objective: A strong association between malignant progression and increased expression of inflammatory and proangiogenic factors has been previously reported in head and neck squamous cell carcinoma (HNSCC). Heterogeneities in vascularization of head and neck tumors have also been shown to affect response to chemotherapeutic agents such as cisplatin in patients. Based on this knowledge, we hypothesized that targeting the tumor vasculature could be of potential therapeutic benefit in head and neck cancers. To test this hypothesis, the antivascular effects of ASA404 (DMXAA), a vascular disrupting agent currently undergoing clinical evaluation, were investigated in a head and neck squamous cell carcinoma HNSCC model.

Results: Treatment of C26 cells and treated with either ODN 2088 or ODN 1826 (injected subcutaneously with 15 nanomoles/mouse on days 0, 6 and 11). Food intake, mouse weight, and tumor size was measured a.o.d. Immediately after sacrifice tumors and quadriceps were collected and stored at -80°C. Final tumor and hind limb weights were measured. Quadriceps lysates were separated by SDS-PAGE and blotted with mouse-specific antibodies to Akt, NF-kB subunit p65, FoxO1, p70S6K, mTOR and actin (Cell Signaling Technology, MA).

Results: Treatment with TLR9 agonist ODN 1826 afforded a statistically significant increase in final tumor weight (minus final tumor weight) for agonist-treated mice versus tumor-bearing (p = 0.013) and antagonist-treated mice (p = 0.012), although the final weight of the agonist-treated mice was less than that of control mice (p <0.001). Treatment with the agonist also reduced final tumor volume to 845±248 mm3 compared to 1919±1246 mm3 for tumor-bearing mice (p <0.05), while antagonist-treated mice had substantially larger tumors 3132±89 mm3 (p <0.001). Agonist-treated mice also showed greater final hind limb mass than antagonist-treated mice (p <0.001). Western blot analysis of quadriceps muscle showed a statistically significant increase in total p65 for agonist-treated and antagonist-treated mice versus control mice (p =0.03 and 0.02), but not compared to tumor-only mice. There was a significant increase in phospho-Akt for antagonist-treated and agonist-treated mice versus control and tumor-bearing mice (p <0.03, 0.03, and 0.05, and 0.01). Most interestingly, a nearly significant increase in phospho-FoxO1 was found for agonist-treated versus control mice (p = 0.07).

Conclusions: Treatment with TLR9 receptor agonist ODN1826 significant-ly reduced cachexia caused by the C26 adenocarcinoma tumor in CDF21 mice, with agonist-treated mice having greater final and hind limb weights than tumor-only or antagonist-treated mice. Treatment with agonist ODN1826 increased survival and reduced tumor volume. Treatment with the TLR9 agonist produced a significant increase in total p65 and phospho-Akt in skeletal muscle versus control mice.
tion was investigated in an orthotopic model of human HNSCC. **Methods:** Eight-to-ten week old athymic nude mice bearing orthotopic HNSCC xenografts (FaDu) were treated with ASA404 (30 mg/kg, i.p.) and changes in tumor vascular function determined using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Intratumoral levels of tumor necrosis factor-alpha (TNF-α) and angiogenesis were also determined using the enzyme-linked immunosorbent assay (ELISA) 3 hours after treatment. MRI data was correlated with estimates of microvessel density (MVD) obtained by immunostaining of tumor sections for the panendothelial cell adhesion molecule CD31. **Results:** DCE-MRI revealed a marked reduction in tumor vascular volume (0.012±0.0021, P<0.0001) twenty-four hours after ASA404 treatment compared to untreated controls (0.172±0.0149). Consistent with previous results, intratumoral TNF-α and angiogenesis were significantly elevated 3 hours after treatment. A marked reduction in MVD (2.075±0.2712, P<0.0001) was also observed in CD31-immunostained sections of tumors obtained from ASA404 treated animals compared to untreated controls (17.13±0.7144). **Conclusions:** Our results for the first time demonstrate potent vascular disruptive activity of ASA404 in an orthotopic human head and neck tumor model. Phase I trials of this agent in head and neck cancer patients should be considered.

**S216: Resveratrol Enhances Etoposide in Merkel Cell Carcinoma**

**Objective:** Merkel Cell Carcinoma is a rare but very aggressive skin cancer of neuroendocrine origin. Chemotherapy is mainly used in a palliative setting. A combination commonly used is cisplatin and etoposide. The purpose of this study was to investigate whether the flavonoids curcumin and resveratrol increase the effect of these agents in vitro. **Methods:** Proliferation assays were performed to assess IC50 values of single agents in the three Merkel Cell Carcinoma lines MCC26, MCC13 and MCC1412. Combinations of equivalent IC50 fractions were analysed using the CalcuSyn software package. A combination of resveratrol and etoposide showed synergism over a wide dose range (1/4 IC50 to 4x IC50). Furthermore, combination of resveratrol and cisplatin resulted in an additive effect. Addition of curcumin to both cisplatin and etoposide showed synergistic cytotoxicity in small doses and an inhibition in higher ones. **Conclusion:** Resveratrol seems to be an attractive substance in the treatment of Merkel Cell Carcinoma as an adjuvant agent to a cisplatin/etoposide regimen.

**Clinical: Skin/Melanoma/Sarcoma**

**S217: Influence of Neck Dissection +/- Radiotherapy on Regional Control in Patients with Melanoma Neck Node Metasasis**

**Objective:** To examine the effectiveness of adjuvant radiotherapy and type of neck dissection on regional control in patients with melanoma neck node metastasis. **Methods:** A retrospective study was carried out in 64 patients treated between 1989 and 2004 for neck node metastasis from melanoma. Twenty-four patients were treated with surgery (S) only; of these patients fifteen underwent a (modified) radical neck dissection (MRND) and nine a selective neck dissection (SND). Forty patients underwent surgery (S) and adjuvant radiotherapy (RT) of the whole ipsilateral neck. Criteria for adjuvant radiotherapy were: 2 or more positive nodes (before 1992: 2 or more positive nodes, extra capsular rupture (ECR), nodes larger than 3 cm or recurrence. Radiotherapy dose was 4-6 times 5 Gray, delivered once a week. Recurrence and survival were calculated from the time of lymph-node dissection. Patients were censored at time of death or last follow-up. Survival curves were constructed using the Kaplan-Meier method. The log-rank test was used for comparison between groups. **Results:** Prognostic factors were worse in the S+RT group than in the S group (2 or more positive nodes 85% vs 38%, ECR 35% vs 8%). With a median follow up of 2.1 years, ipsilateral regional control was in favour of the combined modality group (2 yr regional recurrence was 18% in RT group and 46% in no RT group, p=0.16), despite worse prognostic factors. Ipsilateral regional control was better in both groups (3/40 in RT group and 2/24 in no RT group). Overall survival was worse in the combined modality group (2 yr overall survival was 26% in RT group and 54% in no RT group, p=0.07). The type of neck dissection influenced the risk of ipsilateral regional recurrence in patients treated with surgery only. Ipsilateral regional recurrence was worse after SND in comparison to MRND in this group (4/9 patients after SND and 4/15 patients after MRND, p=0.08). Three of the four recurrences after SND only occurred outside the operated neck. These three patients all underwent a SND of a limited number of levels (2 x level III, 1 x level IVa) for a single positive radical clearance of all regional lymph nodes remains the priority in preventing regional recurrence in the neck. Factors such as extracapsular spread, and large or multiple nodes have been demonstrated to indicate a higher risk of distant spread and overall mortality rather than regional recurrence, and both remain unaffected by the use of adjuvant radiotherapy. **Conclusions:** Ipsilateral neck dissection without radiotherapy for melanoma neck node metastasis leads to a substantial risk of ipsilateral regional recurrence. Therefore, it is indicated to perform a (modified) radical neck dissection in patients who do not receive radiotherapy to improve ipsilateral regional control, even if they have low risk neck disease.

**S218: The Benefit of Adjuvant Post-Operative Radiotherapy to Cervical Lymph Nodes in Cutaneous Melanoma**

**Aims:** To examine the effectiveness of adjuvant radiotherapy in an era of more conservative surgery for neck metastases from cutaneous melanoma. **Methods:** A retrospective study was carried out at the Sydney Cancer Centre and the Sydney Melanoma Unit and the Sydney Head and Neck Cancer Institute. Patients having adjuvant radiotherapy following cervical node surgery for melanoma between 1990 and 2004 who had a minimum follow-up period of 12 months were included. The impact on overall survival, regional control in the relevant node field and loco-regional control was assessed. **Results:** During the study period, 9455 primary melanomas were treated including 856 cases of patients undergoing cervical node surgery, of which 716 met the study criteria. Of these, 129 patients had adjuvant radiotherapy, leaving 587 patients who did not. Patients who had more extensive surgery such as radical neck dissection and/or parotidectomy were more likely to have adjuvant radiotherapy (chi-square, p < 0.0001). 16.9% of patients developed neck recurrence, and both remain unaffected by the use of adjuvant radiotherapy. **Conclusions:** Ipsilateral regional recurrence in patients treated with SND in the RT group was not different from patients treated with MRND in this group (1/12 patients after SND and 5/28 patients after MRND, p=0.6). All these recurrences occurred inside the operated levels. **Conclusions:** Ipsilateral regional recurrence in patients treated with MRND in the RT group was not different from patients treated with MRND in this group (1/12 patients after SND and 5/28 patients after MRND, p=0.6). All these recurrences occurred inside the operated levels. **Conclusions:** Ipsilateral regional recurrence in patients treated with MRND in the RT group was not different from patients treated with MRND in this group (1/12 patients after SND and 5/28 patients after MRND, p=0.6). All these recurrences occurred inside the operated levels. **Conclusions:** Ipsilateral regional recurrence in patients treated with MRND in the RT group was not different from patients treated with MRND in this group (1/12 patients after SND and 5/28 patients after MRND, p=0.6). All these recurrences occurred inside the operated levels. **Conclusions:** Ipsilateral regional recurrence in patients treated with MRND in the RT group was not different from patients treated with MRND in this group (1/12 patients after SND and 5/28 patients after MRND, p=0.6). All these recurrences occurred inside the operated levels.
Sinonasal mucosal melanoma is a rare disease associated with 5/92 and 5/06, 24 consecutive patients treated at a single institution. Our data suggests that the current treatment outcomes, recurrences and survival were evaluated. The patients were restaged at the AJCC staging system using the available clinical and radiological information. Surgical specimens of 31 patients were reviewed by a single pathologist to identify histologic predictors of survival. Results: There were 35 males and 23 females in the group and the median age at presentation was 63 years old. The median follow-up was 20 months with an overall 5-year survival of 41%. 3 patients had a history of cutaneous melanoma and 4 patients had melanosis at presentation. The nasal cavity (57%) and the maxillary sinus (19%) were the most common primary sites. The majority of the patients (91%) had no evidence of regional or distant disease at the time of presentation. Restaging of the primary according to the AJCC system yielded 16 patients (28%) with T1, T19 with T2 (33%), T3 with T20 (20%) and 11 with T4 (19%). T stage was found to be a predictor of outcome (5-year survival: T1 & T2 52.8%, T3 & T4 21.2%; p = 0.0096) but was not related to disease free survival (p=0.92). Tumor pigmentation was a strong prognostic indicator (0% 3-year survival, p<0.001). Pseudopapillary architecture was not related to the overall survival but it was associated with a higher locoregional recurrence rate (p=0.01). Medial maxillectomy was the most common surgical procedure (62%) and was used as part of the treatment in 32%. A total dose of 54 Gy or higher was associated with a lower locoregional recurrence rate (p=0.02).

Conclusions: Our data suggests that the current AJCC staging system is an effective predictor of clinical outcomes. Histologic features such as pigmentation and pseudopapillarity were associated with a higher mortality and recurrence rate, respectively. The use of postoperative radiative therapy improved locoregional control when a dose higher than 54 Gy was administered. The overall survival of our cohort compares favorably with recent international series. Further studies will help define the therapeutic modalities that would maximize outcome and minimize treatment-related morbidity.

5222: COMPLETE SURGICAL RESECTION FOLLOWED BY POST-OPERATIVE RADIOTherAPY IN THE TREATMENT OF HEAD AND NECK MUCOSAL MELANOMA J I.Gomez1, 1Memorial Sloan Kettering Cancer Center, NYC, NY

Objective: To review a single institution's experience on the use of radiotherapy as an adjuvant treatment after complete surgical resection for head and neck mucosal melanoma. Methods: Between 5/92 and 5/06, 24 consecutive patients with head and neck mucosal melanoma underwent complete surgical resection, followed by postoperative radiotherapy at our institution. Median age was 68 years (range: 45-89 years). Sites included as follows: sinonasal (n=22), oral cavity (n=1), and oropharynx (n=1). All patients had stage I disease with only one patient who had stage II disease. In addition to radiotherapy, chemotherapy (cisplatin, temozolomide, and carboplatin) and immunotherapy (mitomycin b + bacille calmette Guérin, and Ganglioside-3 lactone) were also given to 25% and 19.5% of these patients after postoperative radiation, respectively. The majority of the patients were treated with a hypofractionated regimen (n=20) while only 4 patients underwent conventional fractionation. The most commonly used hypofractionated regimen was either 800 cGy x 3 fractions given over 3 weeks or 600 cGy x 5 fractions over 2.5 weeks. Treatment techniques included: conventional (n=11), 3D conformal (n=4), and IMRT (n=9). Prophylactic nodal irradiation was given to none of the patients. Acute toxicities and late complications were graded according to the Common Terminology Criteria for Adverse Events, Version 3.0. Results: With a median follow up of 36 months (range: 15 to 186 months) for living patients, the 3- and 5-year estimates of local progression-free, regional progression-free, loco-regional progression-free, distant metastasis-free, and overall survival were 82% and 63%, 82% and 63%, 83% and 63%, 50% and 38%, 21% and 17%, 41% and 34%, respectively. Median time to local failure (LF) and distant metastasis (DM) was 42.6 and 12.8 months, respectively. Acute toxicities were minimal with 11% complaining of grade 2 mucositis. There was no difference in terms of toxicities among patients who were treated with a hypofractionated regimen versus those treated with conventional fractionation. No late complications related to the optic structures were observed. Conclusion: Radiotherapy given post-operatively to patients with head and neck mucosal melanoma is feasible with minimal toxicities observed. A hypofractionated regimen using higher dose per fraction did not result in unwarranted late complications. Distinct metastases remain the predominant failure pattern. More effective systemic therapy is needed to maximize cure in this cohort of patients.

5223: SENTINEL LYMPH NODE BIOPSY FOR HEAD AND NECK CUTANEOUS MELANOMA A.B.Ermann1, T.M.Johnson1, C.R.Bradford1, 1University of Michigan, Ann Arbor, MI

Objective: To further characterize the reliability of sentinel lymph node biopsy in head and neck cutaneous melanoma. Methods: Three hundred patients with cutaneous melanomas of the head and neck underwent sentinel lymph node biopsy at the University of Michigan between 1997-2007. Detailed histological and clinical data was extracted from a prospectively collected, IRB-approved data set. Of these, 80 were included in a previously published series (Schmalbach et al., 2003.). Results: The present study is an expansion of our previously published dataset with significantly increased patient numbers and substantially longer follow up, making it one of the largest series of head and neck cutaneous melanoma patients who have had sentinel lymph node biopsy reported to date. In the series, 16.8...
Screening for synchronous pulmonary tumours

Carcinosarcomas (spindle cell carcinomas SpCC) are rare. 1882 patients were identified. Sentinel lymph node biopsy in patients with cutaneous melanoma of the head and neck is a safe and reliable strategy to identify a subset of patients who may benefit from therapeutic lymph node dissection and adjuvant therapies.

**Methods:** A retrospective chart review was performed based on CPT codes for parotidectomy and neck dissection. Patients were included if either parotidectomy or neck dissection was performed as part of the treatment for squamous cell carcinoma of the skin. Studies have proven increased survival in patients with mucosal squamous cell carcinoma metastatic to regional lymph nodes with ECS when these patients were treated postoperatively with chemoradiotherapy. ECS in lymph nodes from metastatic squamous cell carcinoma of the skin is considered to be an indicator of aggressive disease, but the effect on survival has not been studied. This study was intended to determine the natural history of squamous cell carcinoma of the skin metastatic to regional lymph nodes with ECS.

Objective: The aim of this study was to elucidate the treatment options and outcome of SpCC of the upper respiratory and digestive tract.

Results: 26 patients were included in the study with a total of 31 procedures. 13 patients underwent parotidectomy and neck dissection at the same setting. Mean age was 73.6 years, and mean follow-up was 24 months. Adequate pathologic data was available from 17 procedures. ECS was noted in 16 of 17 pathologic specimens. The 3-year overall survival was 35%. Regional recurrence occurred in 4 patients who had received not only surgery to the regional nodes, but also radiation therapy. Distant failure occurred in 3 patients all of whom had ECS in regional nodes. Conclusion: ECS in lymph nodes involved with metastatic squamous cell carcinoma is associated with trends in poor overall survival and recurrence regionally as well as distantly. Given that this pathologic finding is such a poor prognostic finding, identification of ECS may warrant aggressive therapy with postoperative chemoradiotherapy.

**Background:** Carcinosarcomas (spindle cell carcinomas SpCC) are rare tumors of the upper aerodigestive tract. The larynx and oral cavity are the most frequently involved sites. There has been much controversy regarding the histological nature and clinical course of these tumors as well as the better choice of treatment. The aim of this study was to elucidate the treatment options and outcome of SpCC of the upper respiratory and digestive tract.

Methods: All medical records of patients with diagnosis of head and neck SpCC in a referral cancer center from January 1, 1996 to December 31, 2005 were retrospectively analyzed. The clinical features, treatment and survival of SpCC patients were evaluated. All patients were staged according to AJCC 013 2002. Results: Of the 56 patients that compose this series, most (83.3%) were males with a mean age of 66 years (range 43-85yrs). Pain, dysphagia and dysphonia were the most common symptoms, the mean duration of symptoms is 6 months. Most patients had history of alcohol consumption and tobacco consumption (67.85% and 82.14%) respectively. As far as the primary site is concerned there were 27 cases (48.1%) of larynx (19/27) and hypopharynx (8/27) and 29 cases (51.9%) of oral cavity (14/29) and oropharynx (15/29). In this series 62.5% of patients had advanced disease at presentation (stages III and IV). Eighteen patients (32.14%) had clinical lymph node metastases at presentation. Occult lymph node metastases was found in 41.17% (7/17) of patients and six (12.7%) patients who underwent radical treatment (surgery, surgery plus radiation, chemoradiation or exclusive radiotherapy) developed regional recurrences. Nine patients (16%) received palliative treatment. Seven patients (3 of the group of oropharynx and oral cavity and 4 of the group of larynx and hypopharynx SpCC) developed distant metastases (12.7%) after radical treatment. The 5-year overall survival (OS) and disease-free survival (DFS) rates were 40.6% and 60.8%, respectively. Although without statistical significance, patients with SpCC of the larynx had a better prognosis in comparison with the other sites (p = .2) (OS 013 larynx 63.7%; hypopharynx 46.8%; oral cavity 36.3%; oropharynx 25.8%). The 5-year OS rate of patients who were treated exclusively by surgery (S) was 68%, in comparison with 40.2% among those who had surgery plus radiation (SR), 41.8% for those who underwent chemoradiation/exclusive radiotherapy (CRT), and 11.4% for palliative radiation (p = 0.01). The DFS rate of S vs CRT = 70%, SR vs CRT = 48,1%, CRT vs 41.5% (p = .001). Conclusion: The high rates of lymph node metastases found in our study strongly emphasizes the role of neck dissection (selective or therapeutic) in the management of SpCC patients. Radical surgical treatment (with or without adjuvant radiation) was an important prognostic factor for improved OS (p = .01) and DFS (p = .02) rates, in our study.

**IMAGING**

**S226: DETECTION OF LUNG TUMOURS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK AT THE TIME OF PRESENTATION**

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Objective of the study: Screening for synchronous pulmonary tumours at initial presentation of head and neck squamous cell carcinoma (HNSCC) is considered important as detection may alter subsequent management. There is currently no consensus regarding best practice. We present the largest series reported of pulmonary screening and comparison of CT and Chest X Ray (CXR). We compare the effectiveness of both modalities and based on our data propose a prognostic screening policy.

Methods: Retrospective review of the findings of thoracic CT and/or CXR performed on all patients presenting to University Hospital Aintree, UK, with HNSCC between January 1996- January 2007. Results: 1882 patients were identified. 1144 had CT, and 742 had CT and CXR. There were 1776 patients with primary tumours and 106 with recurrence. Overall 67 (3.6%) presented with synchronous pulmonary tumours (27 bronchial carcinomas (1.4%), 40 metastases (2.2%), 8 patients found to have a synchronous bronchial primary had concurrent treatment of both tumours. In the subgroup of patients who had both CT and CXR, 43 tumours (5.8%) were detected (bronchial carcinomas (2.6%), metastases (3.2%). The sensitivity for CXR was 61.5% for all synchronous lesions (68% for bronchial tumours, 58% for metastases) compared to 100% for CT. CXR has a positive predictive value of 30.5%, negative predictive value of 98.5% for all primary tumours compared to 50% and 100% for CT respectively. Recurrent disease is a highly significant predictor for both bronchial carcinoma and pulmonary metastases (p = 0.005). When looked at in the context of numbers needed to scan (NNS) to detect 1 tumour, in the T1NO3 group, NNS for metastases = 166, and for bronchial carcinoma=87, overall NNS=70. For other tumour stages NNS are 25.6, 26.3 and 17.5 for T2NO, T2N+ and T4N+ respectively. In the recurrent disease group rT0rT4, NNS ranges from 2.6-13. When looking at site specific data NNS is 4.6, 20.4, 42.2, 43.3 and 57.5 for oesophagus, hypopharynx, oropharynx, larynx and oral cavity respectively. No synchronous lesions were detected in our nasal cavity/paranasal sinus SCC series (n=51).

Conclusions: On the basis of our findings we propose the following screening protocol.Thoracic CT can be applied to all unknown primary site tumours, 12-14 tumours regardless of N stage, loco-regional recurrent disease, where signs/symptoms of neoplastic chest disease exist, and if there are any signs on a staging CT. Given that CXR has a NPV of 98.5% it can suffice as an investigation in T1 disease of any site excluding oesophagus, and potentially all lipp/oral cavity and nasal cavity paranasal sinus tumors. If our series was investigated on this basis there would have been a potential cost saving of £61218 or $120436 (CXR=£18, CT=£160).

**S227: THE ROLE OF IMAGING STUDIES FOR THE DETECTION OF RETROPHARYNGEAL LYMPH NODE METASTASIS IN HEAD AND NECK CANCER**

H. Chu1, I. Park1, J. Kim1, Y. Rho1, D. Yoon1,
Retropharyngeal lymph nodes (RPLN) have received little inves-
tigation as metastatic sites in patients with advanced carcinoma of head and neck. The diagnosis of RPLN metastasis is difficult to evaluate because the location of nodes is beyond the limitation of physical examination or standard neck dissection. The purpose of this study is to investigate the accuracy of imaging studies in determining the presence or absence of metastatic retropharyngeal adenopathy in head and neck cancer patients.

**Methods:** From 1998 through 2006, CT (n=68), MRI (n=54), and/or PET-CT (n=13) images of 68 patients with head and neck cancer were reviewed by one radiologist (D.Y.Y). All patients underwent RPLN dissection. The radiologic findings were compared with the histopathological findings of RPLNs and the results of each modality were analyzed for sensitivity, specificity, positive and negative predictive value, and overall accuracy. There were 52 men and 16 women. Mean age was 59 years (range, 33-81 years). The tumor sites were oropharynx in 27, hypopharynx in 22, oral cavity in 9, larynx in 2, thyroid gland in 6, nasal cavity in 1, and parotid gland in 1.

**Results:** The pathologically positive RPLNs were found in 22 (32.4%) of the 68 patients. A common primary site was oropharynx in 10 patients and followed by hypopharynx in 4, thyroid in 4, and oral cavity, larynx, nasal cavity, parotid gland in the remaining 4. The radiologist correctly read the imaging in 19 of 22 patients with histologically proved metastasis, and 28 of 46 patients with histologic features negative for metastasis. The sensitivity and specificity were 86.4% and 69.9% for CT; 85.0%, 71.3%, 86.0% and 60.9% for PET-CT, respectively. The pos-itive predictive value and negative predictive value were 51.4% and 90.3% for CT; 56.7%, 87.5% for MRI; 40.0% and 93.3 for PET-CT, re-spectively.

**Conclusions:** In this study, we have shown no significant difference between CT, MRI, and PET-CT imaging for detection of RPLN metastasis. High sensitivity and low specificity lead us to overestimate the RPLNs metas-tasis, even including PET-CT. And a trend toward high negative predictive value, these modalities could have a role to prevent needless RPLN dissec-tion in head and neck cancer.

**Ref:** S228: DYNAMIC CONTRAST-ENHANCED MR IMAGING: A RELIABLE DIAGNOSTIC TOOL FOR RECURRENT HEAD AND NECK TUMORS E. Kamel, B. Duvoisin, P. Hauser, L. Borchart, P. Schnyder, P. Pasche, Lausanne University Hospital, Lausanne, Switzerland;

**Aim:** To investigate the role of Dynamic Contrast-Enhanced MR Imaging (DCE-MRI) in the follow-up of patients with head and neck tumors. **Methods:** Twenty-seven patients were recruited. DCE-MRI was performed as a part of regular posttherapy follow-up (n=20) or for clinical suspicion of local disease recurrence (n=7). Axial dynamic T1-weighted fat-sat-urated sequences were performed in a 3-T MR scanner for a total duration of 10 minutes at 12.8 s/interleave with 256×192 matrix and 1-mm slice thickness. The optimal slice was placed in the maximal enhancement area(s) of the tumor bed in all patients. A time-intensity curve was constructed and analyzed. The time to maximal enhancement (Tmax), enhancement ratio at 3 min (ER3min), and washout ratio at 10 min (WR10min) were measured. Per-lesion DCE-MRI findings were correlated with histologic analysis or with clinical and radiological follow-up. **Results:** There was a significant difference between Tmax, ER3min, and WR10min of recurrent lesions and those of posttherapy tissue remodeling (2.2 min, 19%, and 20% vs. 8.3 min, 12%, and 6%, P<0.05). Among 12 recurrent lesions in 9 patients, DCE-MRI detected 11/12 (91%) of these foci. One false negative result was due to microscopic dis-ease residue within posttherapy scar tissue. Two radionecrotic lesions were responsible for false positive DCE-MRI results in 2 patients. These 2 lesions were characterized by indistinguishable Tmax, ER3min, and WR10min from those of recurrent tumor foci. In the remaining 16 patients, true nega-tive DCE-MRI findings were confirmed. Accordingly, the sensitivity, specifici-ty, and accuracy of DCE-MRI were 91%, 89% and 90%, respectively.

**Conclusion:** DCE-MRI can be integrated as a valuable tool in the diagnos-tic workup of patients with or without clinical or radiological suspicion of recurrent head and neck tumors.

**Ref:** S229: PET-CT IN THE MANAGEMENT OF HEAD AND NECK MALIGNENCIES: CLINICAL CORRELATION IMPROVES ACCURACY OF INTERPRETATION M. A. Vargas, D. J. Weyhrich, M. A. Smith, D. S. Oliver, M. J. Odell, N. C. Nguyen, M. M. Osman, St Louis University, St Louis, MO

**Introduction:** Fused positron emission tomography and conventional computer tomography (PET-CT) has seen increasing utilization in the manage-ment of head and neck malignancies because of the ability to provide excellent detection of synchronous tumors of the aerodigestive tract, distant metastasis, minimally positive regional nodal disease and a significant tumor response to therapy. Although PET-CT is a highly sensitive modality in detecting malignancy, there remains a significant incidence of false positivity. The purpose of this study was to review a large series of head and neck cancer patients who had undergone evaluation with PET-CT prior to and after treatment to evaluate the incidence of false positive findings and to evaluate the added value of clinical correlation in improving accuracy of PET-CT scan interpretation. **Methods:** A retrospective review was performed of a series of head and neck cancer patients (n=180) at a single institution who had undergone PET-CT scans (n=702) as an integral part of the patients’ management. All scans were evaluated by experienced board certified nuclear medicine physicians. Specific lesions were considered positive if the final dictated report described them as, “malignant” or “highly suspicious.” Accuracy of the scan interpretation was reassessed after cor-relation with all available clinical data including pathologic findings and clin-ical observations by the treating head and neck surgeons. Approval of the study was given by the University’s Institutional Review Board. **Results:** Of the 180 patients, the majority had tumors of the oral cavity, pharynx and larynx with squamous cell carcinoma as the dominant histology and had stage IV disease and thus received multimodality therapy. When each positive finding on PET-CT was correlated to a histologic sample, PET-CT was truly positive 92% of the time with false positive rate of 65%; 35% of scans were truly negative with a false negative rate of 8%. When PET-CT results were compared with clinical correlation then with histopathologic correlation, the false positive and false negative rates decreased to 14% and 2% respectively. The overall accuracy, taking into account both clinical and pathologic findings in scan interpretation were 94% true positive, 25% false positive, 75% true negative and 6% false negative. **Conclusions:** The increased utilization of PET-CT in the management of head and neck cancer has resulted in increased expertise in interpretation of the scans on the part of both the nuclear medicine and treating physicians. As demonstrat-ed in this study, clinical correlation improves the overall accuracy of PET-CT, sparing patients the potential of a greater number of biopsies that would be required without the added value of clinical input. Without excellent com-munication between the nuclear medicine physician and treating clinician this improvement is not realized.

**Ref:** S230: UTILITY OF FDG PET SCANS ON NODAL STAGING IN PATIENTS WITH SQUAMOUS CELL CARCINOMA IN ORAL CAVITY AND OROPHARYNX M. Kim, Y. Joo, K. Cho, Y. Park, H. Yoo, The Catholic University of Korea, College of Medicine, Seoul Republic of Korea

**Background and Objectives:** Accurate evaluation of cervical lymph node status of squamous cell carcinoma(SCC) of the oral cavity and oropharynx is important to treatment planning and prognosis prediction. In this study, we evaluated the use of FDG PET, CT/MRI for the identification of cervical nodal metastases of SCC of the oral cavity and oropharynx with histologic correlation. **Subjects and Method:** We reviewed 46 medical records, from 2004 January to 2007 July, of patients who underwent of FDG PET, CT/MRI for SCC of the oral cavity and oropharynx before surgery. We interpreted FDG PET, CT/MRI to assess the regional lymph node status. We recorded lymph node metastases according to the neck level system of imaging-based nodal classification. **Results:** Forty-six patients received neck dissection at the time of the primary surgery. Twenty-nine (63.0%) patients had bilateral neck dissections when there was clinical or radiologic involvement of cervical lymph node disease on both sides. Histopathology revealed metastases in 28 of 75 (46 plus 29) dissected neck sides and in 45 of 255 dissected cervical levels. FDG PET had a sen-sitivity of 75.6%, a specificity of 96.7% and had higher sensitivities than CT/MRI for identification of cervical metastases on neck side (26/28 vs. 20/28, p<0.05) and level-by-level (34/45 vs. 26/45, p<0.05) bases. The median SUVmax of pathologically positive node levels was 4.15 (range 1.2-10.8) and that of pathologically negative node levels was 2.12 (range 1.2-5.4). The SUVmax of PET-CT scans and SUVmax of PET-CT scans were considered positive if SUVmax > 2.5. Of 26 positive PET-CT scans, 23 were positive on CT/MRI and of 29 negative PET-CT scans, 23 were negative on CT/MRI. Of 26 positive PET-CT scans, 23 were positive on CT/MRI and of 29 negative PET-CT scans, 23 were negative on CT/MRI. **Conclusion:** The SUVmax of PET-CT scans was significantly higher in nodal metastases than in non-metastatic nodes (p<0.05). This study shows that SUVmax of PET-CT scans is an important modality for con-ducting cervical node evaluation in the patients with SCC in oral cavity and oropharynx.
S231: IS THERE AN ADDITIONAL VALUE OF SPECT/CT OVER LYMPHOSCINTIGRAPHY FOR SENTINEL NODE MAPPING IN ORAL/OROPHARYNGEAL SCC

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Objective: Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma (SCC) has been validated by numerous studies. Lymphatic mapping has been shown to be crucial for detection of sentinel nodes. Previous reports suggest a benefit of combined single photon emission computerised tomography with CT (SPECT)/CT over dynamic planar lymphoscintigraphy alone, especially for carcinomas of the floor of mouth (FOM) with close proximity to sentinel nodes in level I. The aim of this study was to assess whether there was an additional value of SPECT/CT over lymphoscintigraphy alone for lymphatic mapping. Methods: Patients with previously untreated and newly diagnosed early (T1/2) SCC of the oral cavity and oropharynx with no clinical and radiologic evidence of cervical lymph node involvement (cN0) were eligible. Lymphatic mapping consisted of preoperative dynamic planar lymphoscintigraphy and SPECT/CT, and intraoperative use of a handheld gamma probe. The number of hot spots detected by lymphoscintigraphy alone was compared to the numbers of hot spots detected by the addition of SPECT/CT. Results: Between 2000 and 2007 the total number of 95 consecutive patients were enrolled in the study. Thirty-seven patients were assessed by preoperative lymphoscintigraphy alone, and fifty-eight by preoperative lymphoscintigraphy and SPECT/CT. Planar lymphoscintigraphy revealed a median number of hot spots of 2.0 (range 0-5). The addition of SPECT/CT detected a median number of hot spots of 2.0 (range 0-6). Subgroup analysis revealed a median hot spot number in oral tongue lesions of 3.0 by SPECT/CT (range 1-5), compared to 2.0 by lymphoscintigraphy (range 1-4). The median number of hot spots for FOM or oropharyngeal lesions was equal (2.0 and 1.5, respectively) for both methods. Full concordance with respect to the number of hot spots between SPECT/CT and lymphoscintigraphy alone was achieved in forty-seven out of fifty-eight patients (81.0%). In eleven of eighteen patients (19.0%), additional hot spots (one in level Ib, seven in level II, and four in level III) were detected by SPECT/CT. All the additional hot spots were found in the same levels or in levels close to those in which lymphoscintigraphy had already shown hot spots. Subgroup analysis revealed that full concordance was greater for oropharynx (9 out of 10, 90.0%), than for FOM (13 out of 15, 86.7%), or oral tongue (25 out of 33, 75.8%). Conclusions: SPECT/CT for preoperative lymphatic mapping is technically feasible and obviously allows better anatomic localization of sentinel nodes. The median number of hot spots detected by SPECT/CT is not significantly higher than the number detected by lymphoscintigraphy alone. Additional hot spots detected by SPECT/CT were located close to the hot spots already revealed by lymphoscintigraphy, and therefore, probably would have been also detected by the intraoperative use of the gammaprobe. There were no unexpected additional drainage routes. In conclusion, the addition of SPECT/CT is not superior for lymphatic mapping compared to lymphoscintigraphy alone, and does not solve the problem of difficult lymphatic mapping in FOM SCC with level I sentinel nodes.

S232: SCREENING OF HYPOPHARYNGEAL CANCER WITH HOODED VIDEOENDOSCOPY AND NARROW BAND IMAGING FOR ESOPHAGEAL CANCER PATIENTS

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The key to improve the prognosis of cancer is an early detection of the primary lesion. The screening of the high risk patients is important for early detection of head and neck cancer. However, it has been difficult to detect carcinoma in situ during routine endoscopy. We screened the esophageal cancer patients for hypopharyngeal cancer before the treatment and during the follow-up period. Plans for videoendoscopy and narrow band imaging were applied in the outpatient setting. One is a videoendoscopy equipped with a transparent hood at the tip which enables the examination and biopsy of the hypopharynx and cervical esophagus. It allows the wide and clear view in the closed cavities such as pyriform sinus with the outpatient setting. Another is Narrow Band Imaging (NBI) system, which is an optical technique with narrow-band filters emphasizing the microvascular proliferation pattern of early mucosal lesions. This is a type of videoendoscopy and narrow band imaging was applied in the out-patient setting. Both patients with esophageal cancer patients underwent screening videoendoscopy for hypopharyngeal cancer with the hooded videoendoscopy and NBI system. The laryngeal and hypopharyngeal cancers which can be detected with the conventional flexible fiberoscopy were excluded. With these endoscopic systems we diagnosed 3 superficial squamous cell carcinomas, 2 carcinoma in situ, and 2 dysplasias. The lesions were all located at pyriform sinus. The advantage and disadvantage of these endoscopic techniques are discussed. The hooded videendoscopy and NBI system will be a strong tool for the early detection of hypopharyngeal cancers, respectively.

S233: RECISTING THE NECK: INTEROBSERVER VARIABILITY IN THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS FOR HEAD/NECK CANCERS

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Purpose: The previously widespread World Health Organization (WHO) criteria for measuring and reporting tumors have been gradually replaced by the Response Evaluation Criteria for Solid Tumors (RECIST) for purposes of treatment decision-making. There are some indications that the RECIST criteria may not be as reproducible as the WHO criteria(1-3). In this regard, head/neck cancers tend to have ill-defined margins at imaging and may pose a particular problem. The purpose of the study is to evaluate interobserver variability in the use of the RECIST criteria compared to the WHO criteria for reporting head/neck cancers. Methods: All neck CTs obtained between June 30, 2005 and June 30, 2006 for all patients at our institution were obtained. Only those tumors that had not yet had surgery, and that had a pre and post chemoradiotherapy treatment CT scan were included. Two board-certified neuroradiologists blinded to each other reviewed the scans and measured the target lesions using both the RECIST and WHO criteria. Changes in measurements between the pre and post treatment MRIs were categorized for each radiologist into one of four treatment response categories using standard criteria: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD). Weighted kappa values were calculated between the radiologists for the RECIST and WHO criteria, and between the RECIST and WHO criteria for each radiologist. Results: For the pilot data, 9 patients (18 scans) were reviewed, and a total of 24 lesions were measured with an average difference in measurement of 25% between the radiologists. For RECIST, weighted kappa=0.40 with 77.8% agreement between radiologists; WHO, weighted kappa=0.61 with 88.9% agreement between radiologists. For each radiologist, agreements between RECIST and WHO were 94.4% and 88.9% with weighted kappa=0.81 and 0.70 respectively. Conclusion: The pilot data suggest that for head/neck cancers, there is greater interobserver agreement between radiologists reviewing neck CTs when utilizing the WHO criteria (bi-dimensional measurements) as compared to the RECIST criteria. We plan to review and present data for 50+ patients (100+ scans) at the meeting in order to provide validation for the above pilot data. References: 1. King et al. Int J Radiat Oncol Phys. 2007;69(1):148-54. 2. Schwartz et al. Ann Oncol. 2006;17(6):1018-23. 3. Therasse et al. Eur J Cancer. 2006;42(8):1031-9.

S234: AUTOFLUORESCENCE IMAGING AND MOLECULAR MARKERS COMBINED, PROVIDE A ROBUST PREDICTIVE STRATEGY IN ORAL CAVITY MALIGNANCY

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Objective: To develop simultaneous fluorescence imaging and combined reflectance/fluorescence spectroscopy in the oral cavity. In addition, to define a panel of molecular markers that can be used in combination with autofluorescence profiling to predict areas at ‘high-risk’ for local recurrence in oral malignancy. Method: We defined a panel of molecular markers that were upregulated in OSCCs (oral squamous cell carcinomas, 214 samples (surgical margins and corresponding OSCCs) from 35 patients; OR and tumour bank). mRNA expression was quantified using the Human Genome U133A Affymetrix chip. Simultaneous fluorescence imaging and combined reflectance/fluorescence spectroscopy was adapted to be applied in the oral cavity. One to two spots were collected for each patient and 100-300 spectra acquired per spot. Blood oxygenation and blood supply were derived from the reflectance/fluorescence spectra. Auto fluorescence was quantified using the Human Genome U133A Affymetrix chip. Cumulative fluorescence imaging and combined reflectance/fluorescence spectroscopy was adapted to be applied in the oral cavity. One to two spots were collected for each patient and 100-300 spectra acquired per spot. Blood oxygenation and blood supply were derived from the reflectance/fluorescence spectra. Auto fluorescence was quantified using the Human Genome U133A Affymetrix chip.
areas of the oral mucosa (i.e. the mucosa appeared white with light, but had an abnormally low autofluorescence) were biopsied. Immunohistochemistry was used to assess the status of the molecular markers identified as potentially predictive of risk (see above). Results: From 214 samples analyzed a panel of 83 genes was identified as potential markers of local recurrence. From these, 12 markers were found over- or under-expressed in negative surgical margins as well as the corresponding OSCCs and four predictive markers were identified. These included genes involved in cell growth and proliferation, apoptosis and response to DNA damage. We are currently further validating their predictive potential by analyzing additional patient material using quantitative RT-PCR and immunohistochemistry. In dysplastic or malignant lesions the autofluorescence images demonstrated a relatively low autofluorescence level. These results were confirmed by immunohistochemical analysis. The fluorescence integral S1 (blue columns) and S1/S2 (mimicking the imaging setup, dark red columns) were reduced. Interestingly, the parameter S1/S2 was statistically better separated between benign and dysplastic/malignant lesions. The blood supply was increased in malignant lesions. Biopsies were taken from patients with abnormal fluoroscopic readings. These are currently being processed and analyzed using immunohistochemistry and quantitative RT-PCR.

Conclusions: We predict that a combination of molecular analysis and autofluorescence imaging will provide a robust predictive platform for assessment of local recurrence in mucosal oral malignancies. In addition, the spectral data collected will provide an optimization algorithm for the existing imaging technique.

TRANSLATIONAL: OTHER

S235: Deregulated microRNA expression in progressive oral leukoplakia and oral carcinoma N.K.Cervigone1, P.Pintor dos Reis1, N.Naranjo Galloni1, G.Brady2, T.Jurisic3, P.Gullane4, J.Irish4, S.R. Rogatto5, S.Kamel-Reid1, 1Ontario Cancer Institute and University Health Network, Toronto, ON, Canada; 2Faculty of Dentistry, University of Toronto, Toronto, ON, Canada; 3Molecular Medicine, University Health Network, Toronto, ON, Canada; 4Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; 5NeoGene Laboratory, Faculty of Medicine, UNESP, Botucatu, SP, Brazil

Objectives: To examine changes in microRNA expression during the progression of oral leukoplakia and to map the genetic pathways associated with these microRNA changes. Methods: Our sample group included 49 sequential samples from 14 patients: 35 leukoplakic lesions (mild, moderate or severe dysplasia) and 14 same-site oral squamous cell carcinomas (OSCCs). All leukoplakia and OSCC samples were collected retrospectively. A commercially available microRNA microarray (Stratagene) and two normal oral cavity tissues (other sites) were used as baseline controls. First, we assessed the efficiency of quantitative real-time PCR for detection of microRNA (miR) changes using Formalin-Fixed Paraffin Embedded (FFPE) samples. In this pilot study, we examined the expression levels of hsa-let-7a miR. We then assessed the global expression of 384 miRs by quantitative real-time PCR, using the TaqMan Low Density Array (Applied Biosystems). Expression levels were determined using the Delta Delta Ct method of data analysis. miR expression values in leukoplakias and OSCCs were compared using the Binary Tree Structured Vector Quantization (BTSVQ) method for clustering of complex expression data. The predictive miR targets of these deregulated miRs were mapped in pathways using publicly available databases. Results: miR expression in normal oral tongue RNA and normal oral cavity tissues were determined; several miRs were found not to be expressed in the oral cavity. Considering that miRs are tissue-specific, ours is the first reported study showing miR profiles in normal oral tissues. We detected a significant decrease in hsa-let-7a microRNA in leukoplakia and OSCCs as compared to normal control tissues. In addition, global miR profiles (using 384 miRs) classified leukoplakia and OSCC samples into two clusters. We identified two clusters of miRs that were deregulated in progressive leukoplakias; one containing highly expressed miRs and the other containing miRs expressed at low levels. Conclusions: Deregulated expression of hsa-let-7a miR may be an important event during oral tumorigenesis. Abnormal miR expression may lead to the identification of potential miRNA targets, including tumor suppressor genes. The identification of such biomarkers may be used, together with clinical and histological assessment, to help predict which leukoplakias have a higher risk of transformation.

S236: Microvascular changes in oral mucositis S.J.Hamilton1, J.Yoo2, A.Badhwar3, A.Hammond4, V.Venkatesan5, N.Read2, 1London Regional Cancer Program, London, ON, Canada; 2Lawson Health Research Institute, London, ON, Canada

Introduction & objectives: Oral mucositis is one of the most significant toxicities for patients undergoing chemotherapy or radiotherapy for head and neck tumours. Despite the current belief that inflammatory mediators play a pivotal role in the development of mucositis, there remains a lack of effective treatment for this debilitating side effect. The microcirculatory changes which accompany this process have not previously been examined. Orthogonal Polarized Spectral (OPS) imaging is a novel method of evaluating microvascular circulation in real-time. This technology utilizes a non-invasive, hand-held microscope that polarizes and filters light in order to obtain images of the microcirculation. Quantification of inflammatory markers such as red blood cell velocity, aggregation and white blood cell extravasation is then possible. The objective of this study was to demonstrate the microvascular changes which accompany oral mucositis, and to compare these results with traditional mucositis assessment methods.

Methods: A prospective, cohort observational study was performed using OPS imaging to examine the sublingual microvascular changes in twenty patients undergoing radiotherapy or chemoradiotherapy for head and neck tumours. Patients were assessed on a weekly basis throughout the course of their treatment. OPS imaging findings were compared with the Oral Mucositis Assessment Scale, a patient symptom questionnaire and patient bloodwork.

Results: Longitudinal examination of patients undergoing treatment demonstrates that, despite a high level of objective and subjective mucositis, microcirculatory inflammatory changes were significantly present.

Conclusions: This is the first time that the microcirculatory effects of oral mucositis have been directly observed. A lack of vascular response suggests that cell damage comes from direct injury and local cell signalling, rather than from microcirculatory inflammation. This helps to explain why many of the mucositis treatments attempted to date have not been effective, as these interventions often target the vascular inflammatory cascade. These findings contradict the currently proposed mechanism of mucosal damage, and may therefore have an important role in the development of therapeutic interventions.

S237: Bioengineered human salivary gland tissue for the treatment of radiation induced xerostomia C.A.Sullivan1, J.Yoo2, S.Soker1, A.Atal1, 1Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC

Objectives: Radiation therapy for head and neck cancer results in salivary gland cell loss, subsequent salivary gland hypofunction and the clinical condition termed xerostomia or “dry mouth”. Treatment of this condition is limited to administration of saliva substitutes and sialogogues. The transient effect of these medications necessitates frequent administration and systemic effects may be intolerable. Creation of implantable salivary gland tissue that is composed of a patient’s own cells would provide a physiologic solution to salivary gland hypofunction. The objective of this study was to engineer functional human salivary tissue in-vitro and in-vivo.

Methods: Human salivary gland cells were cultured from human tissue, expanded and seeded on biodegradable substrates in-vitro. Substrates seeded with cells and substrates without cells were then implanted in athymic rats. Implants were retrieved at 2, 4 and 8 weeks after implantation for phenotypic and functional analyses. Results: Human salivary gland epithelial cells retained their phenotypic and functional characteristics at all culture stages. Histologically, acinar and ductal structures were observed in-vitro and in-vivo. Immunohistochemical and Western blot analyses demonstrated expression of salivary alpha-amylase protein, cytokeratin specific AE1/AE3, aquaporin-5 water channel protein and and functional proteins occludin, claudin and ZO-1 using cell specific antibodies. Reverse transcriptase polymerase chain reaction was used to confirm gene expression on all control and engineered tissue. Transmission electron microscopy showed morphologic characteristics of secretory tissue. Conclusions: Functional human salivary gland cells can be cultured from human salivary tissue. Salivary tissue bearing functional and morphologic characteristics of secretory tissue can be bioengineered using human salivary gland cells. These data suggest that human salivary tissue engineering could provide a physiologic solution for salivary gland hypofunction in head and neck cancer patients.

S238: Phase III randomized study comparing pilocarpine vs. submandibular gland transfer protocol for management of xerostomia N.Jha1, J.Harris2, H.Seikaly2, D.Williams2, K.Sultanum3, M.Hier3, J.Butler4, P.Kerr4, M.Black3, S.Ghosh5, 1Cross Cancer Institute, Edmonton, AB, Canada; 2University of Alberta, Edmonton, AB, Canada; 3McGill University, Montreal, Quebec, Canada; 4University of Alberta, Edmonton, AB, Canada; 5St. Paul's Hospital, Vancouver, BC, Canada
We conducted a prospective phase III multi-center randomized study to compare the submandibular salivary gland transfer procedure with Pilocarpine for the management of radiation induced xerostomia in head and neck cancer patients. Eligible patients included histologically confirmed squamous cell carcinomas of oropharynx, larynx, hypopharynx, unknown primary with neck nodes, planned radiation therapy volume to encompass 83% 80% parotids and radiation 8350 Gy, age >18, Karnofsky performance 80% 60, no use of sedatives drugs, anti-cholinergic drugs/tricyclics. Patients with carcinomas of nasopharynx, oral cavity, salivary gland, N3 disease, recurrent disease, involvement of bilateral neck nodes, pre-epiploic space or level 1 nodes, uncontrolled asthma, acute iritis, or narrow angle glaucoma were ineligible. Patients were treated either with surgery as prime modality to be followed by radiation treatment with or without chemotherapy or chemoradiation as prime modality of treatment with or without planned neck dissection. Salivary functions were evaluated by measuring salivary flow (baseline & stimulated), University of Washington Quality of Life Questionnaire and salivary scans using sodium pertechnete (Na-99mTcO4-) preoperatively, before radiation treatment, and at 1, 3, 6, 12 and 24 months after radiation treatment. The primary endpoint was the salivary function at 6 months follow up with particular emphasis on the amount and consistency of saliva (sections VIIIA & VII) of the University of Washington Quality of Life Questionnaire.

Results: An interim analysis of 120 patients with a minimum 6 months follow up is reported. Intent to treat and per protocol analysis were performed. Intent to treat analysis of all patients reveals significantly superior results in the gland transfer arm: for median baseline and stimulated salivary flow, p = 0.001 and p = 0.003 respectively, for patients reporting none or minimal xerostomia, p = 0.005 and for consistency of saliva, p = 0.005. Per protocol analysis of 97 patients, reveal significantly superior results in the gland transfer arm: for median baseline and stimulated salivary flow, p = 0.0001 and p < 0.0001 respectively, for quality of life scores, patients reporting none or minimal xerostomia, p = 0.003 and for consistency of saliva, p = 0.01. These significant results have led to premature closure of this study to further accrual, as per the stopping rules of the protocol. Conclusions: Submandibular salivary gland transfer procedure is superior to Pilocarpine in management of radiation induced xerostomia.

MAGE-3 in Upper Aerodigestive Tract Cancer

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Purpose: The MAGE genes are members of cancer tests tumors antigens (CTA) that are frequently expressed in upper aerodigestive tract (UADT) cancers and are cancer vaccine targets. However, quantitative expression analysis and the level of MAGE expression in tumor cells necessary for T cell recognition have not been studied, hindering the selection of appropriate candidates for MAGE specific immunotherapy. Experimental Design: Quantitative RT-PCR (QRT-PCR) was used to evaluate the expression of MAGE-3 in 65 UADT cancers, 48 normal mucosal samples from tumor matched sites and 7 HLA-A*0201+ squamous cell carcinoma of the head and neck (SCCHN) cell lines. Results: HLA-A*0201+MAGE-3 327-279 specific cytotoxic T lymphocytes (CTL) from SCCHN patients and healthy donors showed that the threshold of MAGE-3 expression necessary for CTL recognition in vitro appeared to be > 0.1 times expression of control gene, &223-glucorondinase (GUS). This cutoff level allowed us to estimate that 31 (47%) of the 65 tumors expressed MAGE-3 at levels sufficient for CTL recognition. Furthermore, treatment of MAGE-3 low cell lines expressing <0.1 MAGE-3 with a demethylating agent, 5-Aza-2-deoxycytidine (DAC), increased the expression of the MAGE-3 in all cell lines tested to a levels that resulted in CTL recognition. Thus, a high number of UADT cancers express sufficient levels of MAGE-3 to permit CTL recognition. Conclusion: A novel QRT-PCR assay can assist in the selection of candidates whose tumors are likely to respond to a cancer vaccine directed against MAGE-3. Demethylating agents may increase the number of patients amenable for targeting tumor antigens in vaccine trials.

S240: Quantitative Expression and Immunogenicity of MAGE-3 in Upper Aerodigestive Tract Cancer

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Purpose: The MAGE genes are members of cancer tests tumors antigens (CTA) that are frequently expressed in upper aerodigestive tract (UADT) cancers and are cancer vaccine targets. However, quantitative expression analysis and the level of MAGE expression in tumor cells necessary for T cell recognition have not been studied, hindering the selection of appropriate candidates for MAGE specific immunotherapy. Experimental Design: Quantitative RT-PCR (QRT-PCR) was used to evaluate the expression of MAGE-3 in 65 UADT cancers, 48 normal mucosal samples from tumor matched sites and 7 HLA-A*0201+ squamous cell carcinoma of the head and neck (SCCHN) cell lines. Results: HLA-A*0201+MAGE-3 327-279 specific cytotoxic T lymphocytes (CTL) from SCCHN patients and healthy donors showed that the threshold of MAGE-3 expression necessary for CTL recognition in vitro appeared to be > 0.1 times expression of control gene, &223-glucorondinase (GUS). This cutoff level allowed us to estimate that 31 (47%) of the 65 tumors expressed MAGE-3 at levels sufficient for CTL recognition. Furthermore, treatment of MAGE-3 low cell lines expressing <0.1 MAGE-3 with a demethylating agent, 5-Aza-2-deoxycytidine (DAC), increased the expression of the MAGE-3 in all cell lines tested to a levels that resulted in CTL recognition. Thus, a high number of UADT cancers express sufficient levels of MAGE-3 to permit CTL recognition. Conclusion: A novel QRT-PCR assay can assist in the selection of candidates whose tumors are likely to respond to a cancer vaccine directed against MAGE-3. Demethylating agents may increase the number of patients amenable for targeting tumor antigens in vaccine trials.

S241: A Non-Invasive Diagnostic Technique Using Time-Resolved Laser-Induced Fluorescence Spectroscopy in the Hamster Model

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Background: Preneoplastic and neoplastic lesions of the oral cavity are often difficult to diagnose on clinical examination. Fluorescence spectroscopy and Time-Resolved Laser-Induced Fluorescence Spectroscopy (TR-LIFS) imaging have the potential to provide information about biochemical, functional and structural changes in complex multi-layered tissues that occur as a result of pathological transformation. This study investigates the use of time-resolved laser-induced fluorescence spectroscopy (TR-LIFS) as a potential new tool for non-invasive detection of oral carcinoma in vivo.

Methods: Using the well-described hamster cheek pouch carcinogenesis model, 19 male Syrian hamsters were painted on one side of their cheek with a known carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) until lesions developed. Tissue autofluorescence was induced with a nitrogen pulse laser (337 nm, 1 ns.) TR-LIFS data was collected (360-650 nm wavelength range) from the lesions and the normal contralateral tissue. Additionally, 3 hamsters that had never been exposed to DMBA were included as true normals to control for any bystander effect from painting the contralateral cheek. Parameters derived from both the spectral (intensities from narrow spectral bands) and the time domain (average lifetime) were used for tissue characterization. Hematoxylin and eosin staining was performed. A total of 17 normal sections were analyzed with one section demonstrating hyperkeratosis. A total of 18 tumors were analyzed. There were 6 carcinomas, 9 carcinoma-in-situ, 1 severe dysplasia, and 2 moderate dysplastic specimens. Comparisons between histopathology and the spectroscopic data were made to identify features that resulted in the distinct signatures observed. Features from narrow spectral bands) and the time domain (average lifetime) were used for tissue characterization. Hematoxylin and eosin staining was performed. A total of 17 normal sections were analyzed with one section demonstrating hyperkeratosis. A total of 18 tumors were analyzed. There were 6 carcinomas, 9 carcinoma-in-situ, 1 severe dysplasia, and 2 moderate dysplastic specimens. Comparisons between histopathology and the spectroscopic data were made to identify features that resulted in the distinct signatures observed.
TR-LIFS provides a novel and exciting new technique with the potential to improve our ability to non-invasively determine the histopathology of mucosal lesions. By evaluating both the fluorescence spectrum and the lifetime parameters, we can distinguish the different lesions along the spectrum of oral carcinogenesis in the hamster cheek pouch model. Future studies will aim to translate this technique into human head and neck tissues.

**Objective:** Previous authors have demonstrated that discordance exists between surgeons' interpretations of pathology reports and pathologists' intended meanings. One obstacle to clear communication is the challenging task of reconstructing mental models of surgical pathology specimens from text-based reports. We have designed an interactive three-dimensional pathology visualization/documentation model which is intended to improve clinician understanding of specific anatomic tumor characteristics by supplementing traditional text-based pathology reports. Such a visualization would provide surgeons, radiotherapists, and other clinicians ready access to annotated three-dimensional representations of surgical specimens that can be virtually rotated, manipulated, and magnified. Visual markers inserted by the pathologist would indicate the proximity of tumor margins and would provide the option of viewing additional data, such as digitized histological slides. These markers would improve dramatically upon current text-based reports by visually illustrating the position and orientation of tumor margins within the context of the three-dimensional model.

**Methods:** For proof of concept, a mock tumor was created on the true vocal cord of a porcine larynx using cautery. The specimen was serially sectioned in uniform slices, and the slices were individually photographed. The photographs were used to generate a prototype three-dimensional model. This optical model was aligned against gross MR images of the larynx obtained prior to serial slicing. Digitized microscopic images were captured from a tissue slice which included the mock tumor. Results: We will demonstrate the model visualization by means of a video demo. The demo will show manipulation and rotation of the three-dimensional model, as well as selection of specific areas of interest and examination of related histological data annotated by the pathologist. This manipulation will demonstrate the benefits of visually expressing the location and margins of the tumor in the context of the gross surgical specimen. Conclusions: We believe that key information in pathology reports will be more effectively communicated between pathologists and surgeons and other clinicians through this interactive digital visualization system. We have shown the technical feasibility of using photographic and MR data to generate the three-dimensional model necessary for such visualization and hope to demonstrate the potential benefits of such a model using a video demo. Testing by clinicians will be required to determine the usability of the system.

**References:**

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**Results:**

We will demonstrate the model visualization by means of a video demo. The demo will show manipulation and rotation of the three-dimensional model, as well as selection of specific areas of interest and examination of related histological data annotated by the pathologist. This manipulation will demonstrate the benefits of visually expressing the location and margins of the tumor in the context of the gross surgical specimen. Conclusions: We believe that key information in pathology reports will be more effectively communicated between pathologists and surgeons and other clinicians through this interactive digital visualization system. We have shown the technical feasibility of using photographic and MR data to generate the three-dimensional model necessary for such visualization and hope to demonstrate the potential benefits of such a model using a video demo. Testing by clinicians will be required to determine the usability of the system.
LARYNGEAL CANCER
LOW EXPRESSION OF BAK AND NFkappAB IN ADVANCED
LARYNGEAL CANCER
B.Kumar1, K.G.Cordell1, M.E.Prince1, S.S.Lee1, N.J.D’Silva1, G.T.Wolf1, S.G.Urba1, T.N.Teknos1, T.E.Carey1, C.R.Bradford1, 1University of Michigan, Ann Arbor, MI

Introduction: Evaluation of biomarkers is one approach to better understand the biology of larynx cancer. Prospectively collected biopsy specimens from 58 patients entered into a long-term Phase II trial of organ preservation in advanced laryngeal cancer were evaluated for expression of BAK and NFkappAB and correlations with response to induction chemotherapy and chemoradiation were determined.

Methods: Patients with Stage III/IV laryngeal cancer were treated with a single course of induction cisplatin (100mg/m2 day 1) and 5FU (1000mg/m2/day x 5). Patients achieving >50% tumor reduction received concurrent cisplatin (100mg/m2 days 1, 22, 43) and 70 Gy radiation. Non-responders underwent planned laryngectomy and neck dissection. Tissue microarrays were constructed from pretreatment biopsies and stained for BAK and NFkappAB. Expression of BAK and NFkappAB were evaluated by a pathologist unaware of clinical outcome. The pathologist scored location of expression, proportion and intensity. Correlations were made with response to induction chemotherapy and chemoradiation.

Results: Of 58 patients treated, 20 achieved >50% tumor reduction and received induction chemotherapy (ICF) and concurrent chemoradiation (ICF-IR). 5 patients who failed IC f/u was 75 months (95% CI [63, 81] months). The expression pattern for BAK and NFkappAB was determined. Median f/u was 75 months (95% CI [63, 81] months).

Conclusions: BAK, a pro-apoptotic protein, and NFkappAB, a transcription factor that upregulates expression of genes that suppress apoptosis in cancer cells, are novel biomarkers that predict chemoradiation response in advanced laryngeal cancer in this prospective clinical trial when expressed at low levels. Assessment of biomarker expression on pretreatment biopsy specimens can be used to predict response to induction chemotherapy and concomitant chemoradiation and may someday be used to direct personalized therapies in patients unlikely to respond.

S248: BIOMARKERS IN DYSPLASIA OF THE ORAL CAVITY: A SYSTEMATIC REVIEW
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Introduction: Evaluation of biomarkers is one approach to better understand the biology of larynx cancer. Prospectively collected biopsy specimens from 58 patients entered into a long-term Phase II trial of organ preservation in advanced laryngeal cancer were evaluated for expression of CD24, EGFR, and MDM2 and correlations with outcome were determined.

Methods: Patients with Stage III (n=27) or IV (n=31) laryngeal cancer were treated with a single course of induction cisplatin (100mg/m2 day 1) and 5FU (1000mg/m2/day x 5). Patients achieving >50% tumor reduction received concurrent cisplatin (100mg/m2 days 1, 22, 43) and 70 Gy radiation. Non-responders underwent planned laryngectomy and neck dissection. Tissue microarrays were constructed from pretreatment biopsies and stained for CD24, EGFR, and MDM2. Expression of CD24, EGFR, and MDM2 were evaluated by a pathologist uninformed of clinical outcome. The pathologist scored location of expression, proportion and intensity. Correlations with disease-specific survival were determined. Cox models were used to assess combinations of these biomarkers. Median f/u was 75 months (95% CI [63, 81] months).

Results: Expression of MDM2 in the nucleus was associated with 100% disease-specific survival (p = 0.068). Similarly, expression of CD24 in the cytoplasm was associated with 100% disease-specific survival (p = 0.04). In contrast, expression of the highest intensity of EGFR was associated with the lowest disease-specific survival (p = 0.04).

Conclusions: MDM2, an endogenous suppressor of p53, is upregulated with expression of functional p53. The excellent outcome observed in patients whose tumors express MDM2 suggests that functional p53 status is associated with prolonged disease-specific survival. CD24 is a cell surface marker previously shown to be associated with cisplatin resistance in head and neck cancer and poor prognosis in many other tumor types. Thus the association of cytoplasmic CD24 with favorable outcome demands further investigation. EGFR intensity has been shown to be a marker of poor prognosis in oropharynx cancer and is also a predictor of poor outcome in larynx cancer. These findings demonstrate that assessment of biomarker expression on pretreatment biopsy specimens can be used to predict chemoresistance. Further, pretreatment biomarker profiles may someday be used to direct personalized therapies in patients unlikely to do well with standard regimens.

S247: RESPONSE TO CHEMORADIATION IS PREDICTED BY

Objective: Oral dysplasia is a recognised precancerous lesion diagnosed histologically, with variable progression to cancer. Whilst progression rates are associated with histological grade, it is currently impossible to predict which lesions will progress. Furthermore there is significant inter- and intra-observer variation in grading dysplasia. Therefore there is a need to identify biomarkers predicting progression to cancer. Our study would enable the targeting of these lesions for more aggressive treatment and closer follow-up. We have performed a systematic review and meta-analysis of the accuracy of biomarkers in predicting transformation of oral dysplasia into cancer. Methods: We systematically searched the Cochrane library, MEDLINE, EMBASE, AMED, Cinahl and the Kings Fund electronic databases using the terms: oral dysplasia, leukoplakia, erythroplakia, biomarkers and genetic markers. The following a priori selection criteria were used: longitudinal cohort or case controlled studies of oral dysplasia that progressed to cancer. Cross-sectional studies and studies reporting only on leukoplakia were excluded. Data were extracted by two reviewers. Quality assessment was carried out using validated tools. We assessed relative risk and odds ratios for progression of oral dysplasia to cancer and we performed a meta-analysis where possible. Results: Over 2000 studies were identified by the search process, from which 242 met the criteria and were scrutinised in greater detail. Of these, 206 were excluded because they were cross-sectional in design. A further 16 studies were excluded as a clear histological definition of oral dysplasia was not given. Data were extracted from 20 follow-up studies. The evidence consisted of small clinical outcome studies. Studies were predominantly retrospective in design. In oral dysplasia, loss of heterozygosity (LOH), particularly at 9p/3p loci, predicts progression to cancer (OR 17.9; 95% CI 2.2-140.0). The evidence consisted of small clinical outcome studies. Conclusions: LOH and survivin expression are predictive of advanced oral dysplasia. There are a considerable number of markers that have been studied cross-sectionally, but only a handful have been studied longitudinally. Many methodological limitations have been identified by this review. We recommend that research into this field concentrates in longitudinal design, with

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Recent advances in molecular genetic techniques allow for extensive genetic analysis of a wide variety of human solid neoplasms. Molecular genetic alterations underlying the malignant behavior and progression of HNSCC (Head and Neck Squamous Cell Carcinoma) are not well understood. For HNSCC, no clear correlation between the diverse histologic patterns, anatomic sites, or clinical features and molecular/cytogenetic alterations has been elucidated. LOH (loss of heterozygosity) has been reported in a number of solid neoplasms including HNSCC. We set to determine rate of LOH in 3p,4p,5q,8p,13q,17p,18q, 19q from tumor specimens of tonsil, tongue, and larynx, to correlate LOH with tumor characteristics such as invasive properties, and to determine rate of LOH in specific sites of origin correlate with LOH in diverse manner. Such results may aid in explanation for differential behaviors of HNSCC.

**Objectives:** To determine the expression pattern of hedgehog signalling molecules in HNSCC patients with histologically tumor-free surgical margins for postoperative management. Ideally, those with MRC should receive postoperative radiotherapy, while those with remaining preoperative margins could be omitted if neck staging allows, and routine surveillance will probably suffice. However, there is currently no reliable and simple method for determining of MRC in surgical margins. Here we investigated the suitability of quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) to detect MRC in surgical margins of HNSCC patients.

**Methods:** HNSCC surgical specimens from tonsil, tongue, and larynx were collected from 52 HNSCC patients. Seven patients had histologically tumor-free surgical margins. qRT-PCR of the deep margin samples was negative. In total 24% (10 of 41) of patients developed local recurrences despite histopathologically tumor-free surgical margins. In four of 45 patients with histologically tumor-free resection margins no MRC diagnosis could be performed because immunostaining of the tumor showed no hLy-6D expression and hLy-6D qRT-PCR of the deep margin samples was negative. In total 24% (10 of 41) of the HNSCC patients with histologically tumor-free surgical margins had a qRT-PCR positive test in one or more deep margins, indicating the presence of MRC. Statistical analysis showed significant difference (P < 0.005) in the frequency of cases with hLy-6D positive margins between the groups of patients with tumor-free and tumor-positive surgical margins.

**Conclusions:** This study shows a novel approach for molecular analysis of deep surgical margins. The preliminary data of this study on the application of hLy-6D qRT-PCR to detect MRC in surgical margins of HNSCC patients is promising, but subsequent larger studies with validation by long-term follow-up are needed before the clinical value of hLy-6D qRT-PCR of surgical margins can be really determined.

**Conclusion:** The interaction of Fc fragments with Fc gamma receptors (FcR's) is an essential checkpoint in antibody dependent cellular cytotoxicity (ADCC). For example, polymorphisms in codon 158 of FC3B3RIIIa, which enhance FcR affinity for IgG1, are associated with improved clinical outcome in lymphoma and colorectal cancer patients treated with cetuximab based therapy. The role of ADCC in patients with squamous cell carcinoma treated with cetuximab remains poorly defined. In the current study, we employed three SCCHN cell lines to test the hypotheses that 1. SCCHN is susceptible to Cetuximab mediated ADCC and 2. That efficacy of ADCC is associated with polymorphisms in codon 158 of FC3B3RIIIa. Our results indicate that SCCHN is susceptible to Cetuximab mediated ADCC in vitro. Furthermore, the cumulative percent cytotoxicity for each polymorphism among the cell lines was 58.2% V/ V, 50.6% V/F, and 26.1% F/F (p<0.001), indicating that the presence of an FC3B3RIIIa polymorphic V allele at codon 158 induces enhanced ADCC compared to homozogous F/F. These data have both prognostic and therapeutic relevance and support the design of a trial aimed at determining whether FC3B3RIIIa polymorphisms influence the clinical outcome of patients with SCCHN treated with anti-EF Roy mAbs.

**Conclusions:** Our results suggest that the hedgehog signalling pathway may be involved in the carcinogenesis of MCC and that it can be considered as a potential therapeutic target.

**Objective:** To determine the expression pattern of hedgehog signalling molecules in MCC and that it can be considered as a potential therapeutic target.

**Methods:** Citrus apertus with cartilage invasion based on 2002 AJCC staging criteria from both Maryland School of Medicine, Baltimore, MD; 2 University of Maryland, Baltimore

**Conclusion:** The interaction of Fc fragments with Fc gamma receptors (FcR’s) is an essential checkpoint in antibody dependent cellular cytotoxicity (ADCC). For example, polymorphisms in codon 158 of FC3B3RIIIa, which enhance FcR affinity for IgG1, are associated with improved clinical outcome in lymphoma and colorectal cancer patients treated with cetuximab based therapy. The role of ADCC in patients with squamous cell carcinoma treated with cetuximab remains poorly defined. In the current study, we employed three SCCHN cell lines to test the hypotheses that 1. SCCHN is susceptible to Cetuximab mediated ADCC and 2. That efficacy of ADCC is associated with polymorphisms in codon 158 of FC3B3RIIIa. Our results indicate that SCCHN is susceptible to Cetuximab mediated ADCC in vitro. Furthermore, the cumulative percent cytotoxicity for each polymorphism among the cell lines was 58.2% V/V, 50.6% V/F, and 26.1% F/F (p<0.001), indicating that the presence of an FC3B3RIIIa polymorphic V allele at codon 158 induces enhanced ADCC compared to homozogous F/F. These data have both prognostic and therapeutic relevance and support the design of a trial aimed at determining whether FC3B3RIIIa polymorphisms influence the clinical outcome of patients with SCCHN treated with anti-EF Roy mAbs.

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**Conclusions:** Our results suggest that the hedgehog signalling pathway may be involved in the carcinogenesis of MCC and that it can be considered as a potential therapeutic target.

**Objective:** The hedgehog pathway plays an important role in human development as well as in several types of cancer. The aim of this study was to determine the expression pattern of hedgehog signalling molecules in Merkel Cell Carcinoma (MCC), a rare but very aggressive malignancy of the skin.

**Methods:** We employed a tissue microarray with tripllets of 29 tumor samples of 26 patients with MCC. The slides were analyzed immunohistochemically with anti-Shh, Ihh, PTC, Smo, Gli-1, Gli-2 and Gli-3 antibodies and an immunoreactivity score (IS) was calculated. Results: All of the seven tested antibodies were highly expressed in MCC (mean IS): SHH 90% (7.7), Ihh 83% (8), PTC 83% (9.7), Smo 76% (8.3), Gli-1 76% (4.7), Gli-2 76% (5.3) and Gli-3 83% (8.6).

**Conclusions:** Our results suggest that the hedgehog signalling pathway may be involved in the carcinogenesis of MCC and that it can be considered as a potential therapeutic target.

**Objective:** We previously reported high rates of overall survival (OS) and laryngeal preservation in 2 sequential phase II trials with stage III/IV laryngeal squamous cell carcinoma (LSCC) patients, who attained a > 50% response after 1 cycle of induction chemotherapy (IC), and who were treated with chemoradiation (CRT). Here we report the outcomes of the T4 pts with cartilage invasion based on 2002 AJCC staging criteria from both studies.

**Methods:** Pts received 1 cycle of cisplatin 100 mg/m2 & S-FU
1000 mg/m²/day x 5 days (P+5FU). Pts with > 50% response received chemoradiation (CRT) with 70 Gy & P 100 mg/m², days 1, 22, & 43. Pts with < 50% response underwent total laryngectomy (TL). Final planned tumor assessment by direct laryngoscopy with biopsy was performed 8 wks after CRT. Pts who were histologic complete responders (HCR) after CRT, received 2 additional cycles of P+5FU. Pts with residual disease had planned salvage surgery. Results: 38 T4 eligible pts (16 cartilage invasion alone; 22 extra-articular spread + cartilage invasion) were enrolled; 28 M, 10 F; median age 58; 45% were N0, 55% were N+; site: 24 supraglottic, 12 glottic, 2 hypopharynx. After 1 cycle CT, 30 pts (79%) had > 50% response & received CRT; 7 (21%) had surgery; 1 refused laryngectomy, & 1 was not assessed. After CRT, 26 pts (85%) had HCR, 4 pts (15%) required salvage TL. Of those responding to CRT, 3 pts (7%) eventually required laryngectomy. With a median follow-up of 48 months, 23/38(60%) are alive [21(55%) without disease], 15/38(39%) are dead (10 dead of disease; 5 other causes). Laryngeal preservation was possible in 24/38 (63%) pts. Toxicity: Gr 3/4 granulocytopenia 19%, Gr 3/4 mucositis 49%, 3 yr overall survival (OS) is 76% (95% CI=59%, 87%) and 3 yr disease-free survival (DFS) is 64% (CI=46%, 77%). The laryngectomy-free survival at 3 yrs is 71% (CI=6%,83%). Laryngectomy and G-tube dependency more than 12 months post-treatment was 20% (6/30).

Conclusions: Our results suggest that chemo-selection is a feasible alternative to total laryngectomy as primary treatment strategy for pts with T4 LSCC with cartilage invasion.

S254: COLOUR FLOW DOPPLER ASSESSMENT OF THE ANTEROLATERAL LEG: INTRA-OPERATIVE CORRELATION AND UTILITY ASSESSMENT

K.M.Higgins 1, D.enepeides2, 1Sunnybrook Health Science Centre/Otde Cancer Centre, Toronto, ON, Canada;
2Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Objectives: to assess the accuracy of colour flow doppler in assessment of anterolateral thigh thickness, location and number of musculocutaneous and septocutaneous perforator vessels, and to ensure patency of the source descending cutaneous branch of the lateral circumflex femoral artery. Methods: ongoing case series of patients consented for anterolateral thigh free flap reconstruction underwent preoperative colour flow doppler analysis by a blinded ultrasound radiologist. Patency determination was 100% accurate, and thus allowed potentially to assign the optimum dose of cisplatin and geldanamycin, and their combined. We carried out Immunoblotting of EGFR and Hsp90 signaling mediators in cisplatin sensitive and resistant head and neck cancer cell lines after treating them with cisplatin; geldanamycin and their combinations. Flow cytometry was also carried out in these experimental conditions. Results: Our data indicates that 1. cisplatin sensitivity is cisplatin sensitive and resistant cells, 2. EGFR and Hsp90 interact and can be co-immunoprecipitated, and 3. geldanamycin, an inhibitor of Hsp90, accelerates the degradation of EGFR in cisplatin-resistant cells, leading to both cellular toxicity and significant radiosensitization. Conclusions: These findings demonstrate that EGFR degradation after chemotherapy depends on Hsp90. Furthermore, they suggest that the new generation of geldanamycin analogues that are entering the clinic may potentiate cisplatin-mediated cytotoxicity and radiosensitization via EGFR degradation.

S257: FDG-PET/CT IMAGING DOES NOT IMPACT POST-RADIA

B.J.MOELLER1, T.T.MOELLER1, J.Franklin1, J.Yoo1, D.L.Schwartz1, 1MD Anderson Cancer Center, Houston, TX

Introduction: Retrospective series have suggested that FDG-PET/CT improves assessment of radiotherapy response of head and neck squamous cell carcinoma (HNSSC). We prospectively investigated the contribution of serial pre- and post-radiation FDG-PET/CT scanning to clinical response assessment in advanced stage HNSSC patients. Methods: 105 patients with HNSSC were enrolled onto an IRB-approved trial between November 2005 and August 2007: 93 were available for analysis. Tumors were locoregionally advanced (25% stage III, 75% stage IV) and were mostly of oropharyngeal origin (79%). Each patient underwent serial PET/CT imaging 2 weeks prior to radiation and then 8 weeks posttreatment. Maximum standard uptake values (SUVmax) were recorded for FDG-avid primary and nodal disease on each study and then correlated with clinical response as defined by physical examination, non-PET/CT radiographic studies, and ti-
S258: MOLECULAR IMAGING OF SENTINEL LYMPH NODE METASTASIS USING ONCOLYTIC HERPES SIMPLEX VIRUS-MEDIATED TRANSGENE EXPRESSION

**Objective:** Intervenoperative lymphatic mapping with sentinel lymph node (SLN) biopsy has become the standard approach for evaluating intermedi-ate stage melanoma. The procedure requires surgical resection of the lymphatic basin, lymph node excision and pathologic analysis using serial sec-tioning. Identification of metastatic melanoma by SLN biopsy may require a second operation and extirpation of the remaining nodes. SLN biopsy is a relatively low morbidity technique; however, it still has the potential risks of nerve injury, bleeding and wound complications. Since lymphatic spread of melanoma is uncommon, most patients will undergo surgery for patho-logically N0 disease. Current imaging techniques have a limited sensitivity for detection of micrometastases in lymph nodes. Therefore, there is a need for an effective imaging technique that can accurately identify occult SLN metastases in melanoma patients. **Methods:** The current study is based on the ability of Herpes Simplex Virus 1 thymidine kinase reporter gene (HSV1-tk), to catalyze the thymidine analogue [18F]-2-fluoro-2-deoxy-α-D-arabinofuranosyl-5-ethyl-uracil (18F)-FEAU. The HSV1-tk gene complex was transduced in target cells by herpes viral vector, which has the ability to selectively infect a large variety of cancer cells. After systemic administration, [18F]-FEAU was phosphorylated by the HSV1-tk gene product, which trapped the radiolabeled probe within the cell. The [18F]-FEAU signal was then imaged using a dedicated small animal positron emission tomography (PET) scanner. **Results:** We developed a novel technique for noninvasive molecular imaging of SLNs using HSV1-tk infected cells. In-vivo infection with [18F]-FEAU in mice demonstrated a high level of signal intensity in the sentinel lymph nodes. Furthermore, the [18F]-FEAU signal was found to be stable for several hours after injection. **Conclusion:** The HSV1-tk gene complex is a promising tool for the detection of micrometastases in lymph nodes using molecular imaging techniques.

**Key Points:**
- HSV1-tk gene complex transduced in target cells by herpes viral vector.
- [18F]-FEAU can selectively infect a large variety of cancer cells.
- Signal intensity remains stable for several hours after injection.

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S259: EARLY EXPERIENCE USING TIME- AND SWEPT SOURCE FREQUENCY DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN HEAD AND NECK ONCOLOGY

**Objective:** In vivo detection of dysplastic or early invasive mucosal metaplasia or neoplasm can allow a gamma counter. Measurements of tissue radioactivity revealed more than 2-fold increase of [18F]-FEAU levels in SLNs treated with NV1023 compared with controls. Hematoxylin and eosin staining, immunohistochemistry analysis and X-gal assay confirmed infection and replication of NV1023 in lymph nodes with micrometastases, but not in the normal lymph nodes. **Conclusion:** Our study suggests a novel imaging modality for sentinel lymph nodes using HSV-mediated transgene expres-sion. This noninvasive modality may avoid biopsy for diagnosis, thus direct-ing surgery only to a selective population of patients with locoregional metastases.

**Key Points:**
- HSV-mediated transgene expression for in-vivo detection.
- NV1023 replication confirmed in lymph nodes.
- Noninvasive imaging modality for sentinel lymph nodes.

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S260: MARGINAL MANDIBULAR NERVE INJURY IN NECK DISSECTION AND ITS IMPACT ON PATIENTS PERCEPTION OF APPEARANCE

**Objective:** Marginal mandibular nerve injury is an under-reported complication of neck dissections. It is at risk during the dissection of both level I and II and level I though predominantly level 1. There has been one previous report on the incidence of marginal mandibular nerve injury in neck dissection (1) which described a rate of 21%. The impact of this injury on the patients perception of lip function, smiling and appearance is unknown in patients who had undergone neck dissections. **Methods:** A consecutive series of patients who had undergone neck dissections which incorporated level 1 and level II and level I though predominantly level 1. There has been one previous report on the incidence of marginal mandibular nerve injury in neck dissection (1) which described a rate of 21%. The impact of this injury on the patients perception of lip function, smiling and appearance is unknown in patients who had undergone neck dissections. **Conclusion:** From these results, the method seems to hold great promise for an effective imaging technique that can accurately identify occult SLN metastases in lymph nodes using molecular imaging techniques.

**Key Points:**
- HSV1-tk gene complex transduced in target cells by herpes viral vector.
- [18F]-FEAU can selectively infect a large variety of cancer cells.
- Signal intensity remains stable for several hours after injection.

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**Head and Neck Cancer**

**Proffered Papers**

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**Table:**

<table>
<thead>
<tr>
<th>Site</th>
<th>Endpoint</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tr>
<td>Primary</td>
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<td>77.8</td>
<td>87.2</td>
<td>41.2</td>
<td>97.1</td>
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<td>90.1</td>
<td>41.7</td>
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<tr>
<td>Nodal</td>
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<td>57.1</td>
<td>78.5</td>
<td>22.4</td>
<td>94.4</td>
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<tr>
<td>&lt; CR by CT</td>
<td>83.3</td>
<td>62.7</td>
<td>22.5</td>
<td>97.4</td>
<td></td>
</tr>
</tbody>
</table>

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**Note:** The table shows the sensitivity, specificity, PPV, and NPV of SUVmax thresholds for primary and nodal disease. The SUVmax values were significantly higher for both primary and nodal disease (P < 0.05). ROC analysis demonstrated that SUVmax thresholds of 6.0 for primary tumors and 3.0 for nodal disease yielded the best PET/CT restaging accuracy. However, post-radiation CT imaging yielded similar predictive value (see table). Every patient shown by SUVmax threshold to have an incomplete response to radiation was identically identified by conventional restaging methods. The data suggest that serial FDG-PET/CT does not add to conventional post-radiotherapy response assessment in patients with locally advanced HNSCC, particularly disease originating from the oropharynx. Further investigation is warranted to define the optimal role, if any, for PET/CT in assessment of radiation response across disease subtypes and presenting stages of HNSCC.
patients alive and eligible. A significant proportion of patients had bilateral
al neck dissection in which case both sides were assessed individually. One
patient had a deliberate sacrifice of the marginal mandibular nerve. The
rate of lower lip asymmetry was 20%. The majority of these injuries were
grade II (80%) and 20% were grade III. There were no grade IV, V or VI
injuries. The patients subjective perception of lip function and smile aesth-
etics differed significantly from the clinicians objective assessment. A similar
proportion of patients with grade II and grade III injuries considered
themselves to be disfigured. Patient perception of smile aesthetics relates strong-
ly to dental status. Conclusions: Asymmetry of lower lip function follow-
ing neck dissection is relatively common despite efforts to preserve the mar-
ginal mandibular nerve. It is possible that the deranged function of the
platsyma and cervical branches of the facial nerve are responsible for a
proportion of these patients deformity. The patients perception of injury
differs from that of the clinician and is more closely related to overall oral
function and dental status. This study provides the basis for investigation
of the various methods of nerve preservation. 1. Nason RW et al. Clinical
observations of the anatomy and function of the marginal mandibular

S261: THE INFLUENCE OF PASSIVE VS SUCTION DRAINAGE ON COMPLICATIONS FOLLOWING NECK DISSECTION
M.D. Batstone1, R.J. Shaw2, J.S. Brown2, E.D. Vaughan2, D. Lowe2,
S.N. Rogers1, 1University Hospital Aintree, Brisbane, Australia;2University Hospital Aintree, Liverpool, United Kingdom

Objectives: Drainage following neck dissection is considered mandatory
to prevent haematoma formation and allow skin flaps to adhere to underly-
ing tissues. It is considered necessary for the use of suction drains
however in cases where microvascular free tissue transfer is undertaken.
Case reports have described pedicle damage and flap loss secondary to
interference between the drain and either the anastamosis or pedicle (1). Previous retrospective comparisons have demonstrated a trend towards
increased infection rates with passive drains when compared to suction
drains but the difference did not achieve statistical significance (2). The
objectives of this study were to undertake a prospective non randomized
comparison of passive and suction drains following neck dissection with
and without free flap reconstruction. Methods: A prospective audit of all
patients undergoing neck dissection was undertaken over 8 months at the
regional head and neck centre. The primary outcome measure was healing
of the neck wound without breakdown. Secondary outcome measures were
infection requiring treatment with antibiotics, haematoma formation, fistula
formation and flap loss. Other demographic and surgical details were also
compared. All assessments were undertaken by a single clinician. Both pas-
sive and suction drains were in use at the time of the project. Results: 57
patients (age range 23-89) underwent 72 neck dissections in the 8 month
period. Of the 72 sides, 18 had passive drains and 54 had suction drains.
There were 4 complications in 3 cases which were fistulas but was unrelated
to the drain. The differences in antibiotic treated infection rate and haematoma forma-
tion were not significant. The neck failed to heal primarily in 54% of
patients with a passive drain and in 6% of patients with a suction drain (p=
0.0019). A logistic regression analysis of other possible contributory fac-
tors was undertaken. Discussion: There is a marked difference in neck
healing when passive and suction drains are used. This could be related to
the inability of passive drains to eliminate dead space between the skin flap
and the neck or bacterial migration. Suction drains should be used in all
cases unless it is physically impossible to secure them away from free flap
pedicles. On occasions multiple suture loops should be used to prevent
drain migration. 1. Riaz M, Khan K, Leonard AG. Complications associat-
ed with suction drains after microvascular anastomosis. Microsurgery
cal audit on the effect of suction drainage on microvascular anastomosis.
J Craniomaxfac Surg 2001;29:298-301.

CLINICAL: RECONSTRUCTION II

S262: MANDIBULAR RECONSTRUCTION WITH AUTOLOGOUS FREEZE-TREATED BONE AFTER MALIGNANT TUMOR RESEC-
TION. A PROSPECTIVE STUDY OF 72 CASES
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S.Colombo1, S.Riccio1, M.Squadralli1, 1National Cancer Institute,
Milano, Italy

Objectives: In the seventies of last century some experimental and clinical
works demonstrated the possibility to replace the resected mandibular seg-
mant involved by cancer in its anatomic position after immersion in liquid
nitrogen in order to clean it of viable tumor cells. Of course, this method of
reconstruction may be applied in patients with bone invasion not allowing a
marginal mandibulectomy, but without a massive infiltration that does
not leave a reasonable thickness of bone. Methods: We reviewed the
charts of patients who underwent a resection of large malignant tumors of
the oral cavity and/or oropharynx with segmental mandibulectomy and
reconstruction with autogenous frozen mandibular graft at the National
Cancer Institute of Milan. Surgical Technique: A standard en block
reseact of the tumor in order to facilitate the safe and reliable segmen-
tal mandibulectomy is performed. After removal of the specimen, all soft
tissues are sharply dissected from the bone. The mandibular segment is then
frozen by immersion in liquid nitrogen for 10 + 10 minutes. During these
procedures, another surgical team is harvesting a flap for soft tissues recon-
struction and to cover the mandible. Results: From January 1991 to December
2002, 72 patients with large oral or oropharyngeal cancer had their
segmental resected mandible reconstructed with autologous freeze-
treated bone. A direct suture of the mucosa was possible in only 4 cases.
Soft tissues were reconstructed with a pedicled pectoralis major muscu-
losap in 17 patients, with a forearm free flap in 18 patients, and with
a forearm free flap plus radial peristem in 33 cases. Twenty-six patients
underwent postoperative radiotherapy. Thirty-five patients underwent a
resection of the mental arch of the mandible, while in 37 cases there was
a lateral invasion of the mandible. The overall local-regional cure rate was
61.1%. Forty-one patients (56.9%) retained their autologous mandibular
graft. In 31 cases there was a dehiscence of intraoral closure, with subse-
quent infection and removal of the bone graft. Lateral resections achieved
a better success rate in comparison to anterior resections (75.7% versus
37.1%), and small soft tissues flaps had a higher success rate compared to
the use of suction drains only in 3 of 4 cases. The pedicled pectoralis major flap achieved the worst
result (35.3%) in comparison with forearm free flap (66.7%), or forearm
free flap with radial peristem (60.6%). Postoperative radiotherapy
decreased the success rate (40.0% versus 69.1%). All 4 pre-irradiated
cases had an oral dehiscence with infection and bone removal.
Conclusions: Reconstruction of the mandible with autologous frozen bone
is an interesting alternative to more sophisticated methods. It is time and
cost sparing in comparison to fibula or iliac crest flaps, and it allows the
use of the best flap for soft tissues reconstruction. However, in spite of any
intraoral reconstruction the success rate is not stirring. In our opinion this
type of mandibular reconstruction must be reserved to patients with lateral
tumors, with poor prognosis or severe comorbidities not allowing more com-
plex bone reconstruction. It must not be applied in patients with recurrence
after radiotherapy.

S263: BONE IMPACTED FIBULA (BIF), A NEW TECHNIQUE OF INCREASING BONE DENSITY FOR PLACING DENTAL IMPLANTS
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Introduction: The principal advantage of osseous free flaps in head and
neck reconstruction is potential of implant placement implants which would
facilitate oral or craniofacial rehabilitation. The fibula is the most commonly
used bone in the reconstruction of mandibular and maxillary defects after
cancer ablative surgery. The bone density of most fibular free flaps is usu-
ally sufficient to place implants but the bone stock can be diminished in
some head and neck cancer patients because they tend to be at smokers,
elderly, malnourished and have significant peripheral vascular disease.
The fact that the fibular marrow becomes deficient in bone with age also makes
osteointegration of implants more challenging. At the University of Alberta,
we have developed a new technique to increase the bone density at the
time of free flap transfer in order to facilitate post operative implantation.
We use bone chips from the discarded fibula and implant them in to the
hollow marrow of the portion of the bone used for the reconstruction.
Objective: To assess the the modification of bone impaction of the fibula
on: 1) Bone density of the fibula free flap postoperatively, 2) Ease of place-
ment and retention of implants. Study Design: Prospective cohort study.
Methods: 22 patients with a malignant tumor of the upper or lower jaw who
underwent maxillary or mandibular reconstruction with fibular microvascular
free flaps were included in the study. Fibular bones impacted with autologous bone were compared to unmodi-
fied fibular bones. Bone density was measured from post-operative CT
scans, and the ease and retention of implant placement was assessed by
measuring the degree of vibration at the time of the implantation. Results:
Bone density in impacted fibulas was found to have a higher density as
compared to the unmodified fibular free flaps. Lower degree of dental
implant vibration was observed in the bone impacted fibulas as compared to
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to unmodified fibulas. All modified fibular free flaps survived. Conclusion: Bone impaction fibula (BIF) modification of osseus free flaps, presented for the first time in this paper, increases bone density and facilitates the primary osseointegration of implants.

S264: MICROVASCULAR RECONSTRUCTION OF THE MANDIBLE: CAN FIXATION BE TOO RIGID? E.A. Zoumalan 1, D.Hirsch 1, J.Levine 1, P.Saadah 1, 1New York University, New York, NY

Objective: To determine whether stress shielding reconstruction plates increase bone resorption. Prior studies by Hidalgo and colleagues have reported that a fibula flap used for mandible reconstruction preserves sufficient bone mass over time to support osseointegrated implants. Their group used miniplates for mandible fixation. As other centers, including the authors' own, utilize reconstruction plates for fixation, an unresolved question has been whether stress-shielding reconstruction plates lead to increased bone resorption in the fibula with time. This is important since it may adversely affect the success of dental rehabilitation. The authors investigated this possibility in a group of patients who underwent fibula free flap mandible reconstruction for benign diseases, thereby obviating the confounding effects of irradiation. Methods: A retrospective analysis of 70 fibula free flap mandible reconstructions performed over the last 10 years in a single institution revealed 7 patients (10%) with indication of miniplates as a second fibula flap. No other complications were noted. An average of 3 osteotomies (range: 2-4) of the fibula were performed in situ on the fibula under the pre-bent plate. This allowed 100% accuracy in maintaining preoperative occlusion and in accurately conforming the fibula flap to the extirpative defect. In this series, bone height was maintained at 2 months postoperatively and at 1 year postoperatively. Results: Six of seven fibula flaps survived; one flap failed and was salvaged with a second fibula flap. No other complications were noted. An average of 3 osteotomies (range: 2-4) of the fibula were performed in situ on the fibula under the pre-bent plate. This allowed 100% accuracy in maintaining preoperative occlusion and in accurately conforming the fibula flap to the extirpative defect. In this series, bone height was maintained at 2 months postoperatively and at 1 year postoperatively. Seven flaps survived; one flap failed and was salvaged with a second fibula flap. No other complications were noted. An average of 3 osteotomies (range: 2-4) of the fibula were performed in situ on the fibula under the pre-bent plate. This allowed 100% accuracy in maintaining preoperative occlusion and in accurately conforming the fibula flap to the extirpative defect. In this series, bone height was maintained at 2 months postoperatively and at 1 year postoperatively.

S266: A PROSPECTIVE ANALYSIS OF FACTORS PREDICTING MORBIDITY IN MICROVASCULAR FREE FLAP RECONSTRUCTION OF THE HEAD AND NECK

Objective: The purpose of this study was to determine whether perioperative clinical and treatment-related variables predicted morbidity in patients undergoing microvascular free flap reconstruction of the head and neck. Methods: Demographic, laboratory, perioperative and anaesthetic data recorded prospectively in 803 patients undergoing microvascular free flap reconstruction of the head and neck between 1999 and 2007 were evaluated using univariate and multivariate analysis to determine predictors of morbidity and hospital stay. Results: Two hundred and fifteen patients (27%) developed major complications. Predictors of major medical complications were ASA class, alcohol excess, increasing age, tracheostomy and crystalloid replacement. Predictors of major surgical complications were preoperative hoemoglobin, preoperative chemotherapy, Kaplan-Feinstein index score, and smoking. Predictors of prolonged hospital stay included increasing age, smoking, alcohol abuse, weight loss, preoperative haemoglobin, duration of anaesthesia, ASA grade, and Kaplan-Feinstein index score. Conclusion: We have demonstrated that several variables are associated with an increased risk of development of major complications following free flap reconstruction of the head and neck. Although many of these variables are irreversible, they aid risk stratification of patients undergoing free flap reconstruction of the head and neck, and assist clinicians in making treatment decisions, consenting patients, and providing patients with realistic expectations regarding their perioperative course.

S267: THE INCREASING USE OF DOUBLE FREE FLAP RECONSTRUCTION: INDICATIONS, CHALLENGES, AND PROSPECTIVE FUNCTIONAL OUTCOMES

Objective: Although most head and neck defects can be reconstructed utilizing a single free tissue transfer, the use of two free flaps is indicated for large tissue defects or for composite tissue requirements that cannot be met with a single free flap. In conjunction with a review of the English literature, we present a retrospective analysis of double free flap reconstructions in management of large head and neck defects. Methods: A 5-year retrospective chart review was conducted in a large head and neck oncology program in a tertiary care hospital. All patients receiving double free flap reconstruction of head and neck defects were included. The indications for, and challenges of, double free flap head and neck reconstruction were reviewed. In addition, prospectively collected functional data was analyzed for this subset of patients. Results: A consecutive series of 35 patients (24 males, 11 females, mean age 57.79 years) treated during July 2002 to Sept 2007 were included. Indications for surgery were squamous cell carcinoma (71.43%), adenoid cystic carcinoma (8.57%), and functional reconstruction (5.71%). The most common double free flap combination included an osteocutaneous free flap with a fasciocutaneous free flap (88.57%), utilizing fibular (93.55%) and scapular (6.51%) osteocutaneous free flaps with radial forearm (74.19%), anterolateral thigh (22.58%), and rectus abdominus (3.23%) fasciocutaneous free flaps. Complications were encountered in only two patients (hematoma and venous thrombosis), and the overall free flap success rate was 97.14%. The mean operative time was 13 hours 10 minutes Objective evaluation of functional outcomes by speech language pathologist demonstrated single-word intelligibility in 74.29% of patients, and sentence intelligibility in 85.71% of patients. Modified barium swallows of liquid, pudding, and cookie consistencies revealed no evidence of laryngeal penetration for swallowing liquid consistencies in 71.43% of patients, pudding consistencies in 88.57% of patients, and cookie consistencies in 94.29% of patients. Conclusions: We have demonstrated that with prop-

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The objective of this study is to examine the association of prior radiation with concomitant intraarterial chemotherapy (RADPLAT) with complications following microvascular reconstruction. The goal is to determine if arterial vessel damage from intraarterial chemotherapy within recipient neck vessels results in increased surgical morbidity during microvascular surgery. Methods: This is a retrospective cohort study, performed at a tertiary care academic referral center. Records of patients with Stage IV Squamous Cell Carcinoma of the Head and Neck who were treated with primary radiotherapy with concomitant intraarterial chemotherapy, RADPLAT, were included in the study. Patients of interest were those who subsequently underwent oncologic surgery and/or microvascular reconstruction. The main outcome measures were microvascular complications, specifically need for additional surgical procedures, reasons for surgical procedures, and flap loss. Additional surgical complications, specifically wound breakdown, infection, and fistula were also recorded. Results: Between 1996 and 2002, 86 patients were treated with RADPLAT. 34 patients subsequently underwent oncologic surgery and/or reconstruction. 24 patients underwent planned neck dissection for persistent neck disease, with 4 patients undergoing salvage laryngeal surgery. Seven patients had 8 free flaps either for reconstruction after additional oncologic surgery or for sequelae of prior treatment such as persistent fistula or osteoradionecrosis. Wound breakdown and/or fistula occurred postoperatively in 4 of these patients. 3 patients required return to surgery in the immediate postoperative period for arterial bleeding or arterial insufficiency, with one arterial related flap loss. Conclusions: While wound complications are to be expected following treatment with any chemoradiotherapeutic regimen, microvascular reconstruction following RADPLAT appears to result in a high number of arterial related complications.

**Laser and Other Physical Therapies**

S5271: IMPACT OF RESSECTION MARGINS IN EARLY GLOTTIC CANCER TREATED BY CO2 LASER ON LOCAL CONTROL, AND ORGAN PRESEATION M.A.Massaro1, L.Calabrese2, G.Giugliano1, M.A.Massaro1, L.Santoro1, F.Maffini1, F.Chiesa1, 1European Institute of Oncology, Milan, Italy

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  - S270: MICROVASCULAR RECONSTRUCTION IN THE SETTING OF PRIOR RADIATION WITH CONCOMITANT INTRAARTERIAL CHEMOTHERAPY (RADPLAT)

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Objective: To evaluate potential impact of resection margin’s status on local control in patients treated with endoscopic CO2 laser surgery for early glottic cancer. Methods Design: Single institution prospective non-randomized study. Setting: European Institute of Oncology (IEO), Milan, Italy. Patients: Between May 1999 and October 2005, 318 consecutive patients with an early squamous cell carcinoma (SCC) of the vocal cord underwent endoscopic laser surgery at IEO. Among them 276 had an endoscopic approach and 42 a transoral approach. Results: Out of 74 patients, 5 had a second glottic primary following a laryngeal open surgery. Interventions: Inclusion criteria were cTis, cT1, or cT2, no previous laryngeal treatment, no contraindications to general anesthesia, and signed consent. Surgical technique (according to the European laryngological classification) was type I: V-wardectomy. Resection margins were stained with indigo carmine at the time of resection. The distance between them and the tumour edge was measured. They were defined negative (> 1 mm from the tumour edge), close (< 1 mm) and positive (presence of tumour tissue on resection margins). Patients with clear margins, and those with IN on the margins underwent clinical check-up (every three months during the first year, every four months in the second year and every 6 months later on). Patients with one positive margin underwent a new resection 30–40 days later, and patients with more than one margin underwent a postoperative radiotherapy. Results: The 276 untreated patients (F: 24 and M: 252) were included in this study. Hundred-nine-ty-three out of 276 had a previous vocal biopsy positive for SCC and 83 were classified cTis-T2 on the basis of a clinical and histological evaluation. Seventy-two patients underwent microsurgery, 82 type II, 103 type III, 24 type IV and 51 patients type V. Status of resection margins were negative in 174 cases; close in 36, positive in 57 (26 one positive margin and 31 more than one). Margins were by IN in 6 patients and not evaluable in 3. Forty-six patients (17%) were classified pT0, 34 (12%) pTis, 115 (27%) pT1a, 35 (12%) pT1b, 37 (12%) pT2 and 9 (3%) pT3. Thirty-six patients (12%) with multiple positive margins underwent postoperative radiotherapy and 38 (12%) with one margin involved underwent a new laser surgery. The median follow up was 54 months (24-100). Local recurrences developed in 28 patients (10%) and regional recurrences in 2 (1%). Eighteen patients developed a second primary (7%). Eleven recurrences underwent a new laser surgery, 3 laser surgery and radiotherapy, 2 radiotherapy, 1 subtotal laryngectomy, 11 total laryngectomy, and 2 neck dissection. Five patients died of laryngeal cancer. Main-outcome: Five-year actuarial recurrence-free survival, disease specific survival, overall survival and organ preservation rate were respectively 90%, 98%, 88% and 96%. Conclusions: In our series CO2 removal of an untreated early glottic cancer can be often considered complete when resection margins are a few millimeters far from the tumour edge, at histological examination. Biological and molecular evaluation of margins could achieve further improvement in local control.

S272: PHONOSURGICAL TREATMENT OF EARLY GLOTTIC CANCER: INNOVATIONS THROUGH THE PAST 15 YEARS
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Endoscopic treatment of glottic cancer was established in 1886 as a microring procedure. It was perfected as a bimanual suspension laryngoscopic intervention in 1920s. This was further advanced in the late 20th century by magnification provided by the surgical microscope, and preciser laser surgery. The classic treatment of supraglottic carcinomas is either supraglottic laryngectomy, radiotherapy or both. Laser endoscopic excision (called “laser vestibulectomy”) represents another possibility for the treatment of such tumours. The aim of this large retrospective study was to assess the feasibility and the results of this technique and to compare it to standard therapeutic regimens. Although some would perceive these innovations as problematic oncologically, this series established safety of these phonomaterial innovations. Taken together, surgical innovations over the last 15 years justify a reappraisal of the commonly-held approach of primarily employing radiotherapy for early glottic cancer thereby preserving this valuable single-use cancer treatment.

S273: FUNCTION PRESERVING TRANSORAL LASER MICRO-SURGERY (TLM) FOR CANCER OF THE ORAL CAVITY
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Objectives: Cancer of the oral cavity poses special therapeutic challenges. Open surgery often results in a significant impairment of swallowing and speech function and therefore reduces quality of life. Purpose of this study was to assess the viability of transoral laser microsurgery (TLM) as a tissue sparing and thus function preserving surgical alternative to standard treatment and to compare its oncological and functional results to those of open surgery and radio(chemo)-therapy. Methods: A retrospective chart analysis was carried out. Patients with previously untreated cancer of the oral cavity were eligible for inclusion. Exclusion criteria were pre-treatment, simultaneous second primary cancers and N3 neck disease. 180 patients matched the inclusion criteria and were treated by TLM with or without selective neck dissection and/or postoperative radio(chemo)-therapy. Results: All 180 patients were treated by TLM. 75% received a selective or modified radical neck dissection, 34% had an adjuvant radiotherapy. The median follow-up period was 60 months. Overall survival (5-year Kaplan-Meier) ranged between 74% for stage I and 29% for stage IV tumors, whereas recurrence-free survival (5-year Kaplan-Meier) ranged between 73% for stage I and 47% for stage IV tumors. Postoperatively, no nasogastric feeding tube was required by 54% of the patients, only 2% required a permanent gastrostomy tube. Conclusions: Transoral Laser Microsurgery is a valid and cost-effective alternative in the treatment of oral cavity cancer. Oncological results are comparable to standard therapeutic regimen, while functional results tend to be better.

S274: LASER VESTIBULECTOMY FOR SUPRAGLOTTIC CARCINOMAS: FEASIBILITY AND LONG TERM RESULTS
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Objective: The classic treatment of supraglottic carcinomas is either supraglottic laryngectomy, radiotherapy or both. Laser endoscopic excision (called “laser vestibulectomy”) represents another possibility for the treatment of such tumours. The aim of this large retrospective study was to analyse the feasibility and the results of this technique and to compare it to classic ones. Patients and Methods: Between 1990 and 2006, 64 patients suffering from supraglottic carcinomas have been treated by “laser vestibulectomy”. The sex ratio was 3 men for 1 woman and the mean age was 62 years. There were 10.9% of Tis, 31.3% of T1, 40.7% of T2 and 17.2% of T3. The large majority of them were N0 (85.9%) but there were also 4.8% of N1 and 9.4% of N2. 53% of the population received also a neck dissection. Radiotherapy was proposed for patients with N+ (23.4%) or with positive margin (3.1%). Results: The mean hospital stay was 11.3 days, 1 patient is dead 12 hours after the treatment for massive haemorrhage. No patient needed tracheotomy. The 5-years adjusted survival rate was 95.6%. The overall 5-years survival was 62.4% and the reason of death was mostly another cancer. The local control was 91%. 11% of the patients have presented a nodal recurrence and 2% a metastatic recurrence. 2 of the 6 patients with local recurrence have been treated successfully: one with a second laser excision and one by partial laryngecto-
my. The survival or the local recurrence rate were not significantly influenced by sex, the T stage or the N stage. Conclusion: The “laser vestibulectomy” appears to be a good alternative for the treatment of supraglottic carcinomas. This laser procedure offers the same local control rate than supraglottic laryngectomy and a better one than radiotherapy alone. The time of hospitalisation is shorter and the complication rate is smaller than with other treatments. In this way, this laser endoscopic approach has to be developed.

S275: ENDOSCOPIC CO2 LASER SUPRAGLOTTIC LARYNGECTOMY(ELSL): MULTICENTER ANALYSIS OF 144 CASES

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Objective: The purpose of this study was to evaluate reproducibility of Endoscopic approach for the treatment of Supraglottic carcinoma (SC), surgical complications, oncological and functional outcome. Methods: From September 2006, we prospectively and retrospectively included and reviewed all the medical records of one hundred and forty-four patients with SC treated by ELSL in Seven centres of French cooperative study group of Head and neck tumors GETTEC. The main outcome measures were: the type of the surgery according to the tumors location, necessity of tracheotomy during the procedure, the management of the neck, post operative complications, mean postoperative swallowing time, mean post operative hospital stay, local and regional control, overall survival. Multivariate analysis was used to examine the relative impact on outcome of the variables demonstrated to be statistically significant in univariate analysis. Results: There were 28 females and 116 males, with a mean age of 62,2 years (30 to 86y). The ELSL was limited (to the free edge of epiglottis, ventricular or arytenoids) in 23 (16%) patients, to one lateral part of the epiglottis in 41(28%), passing through the pre-epiglottic space in 36(35%), extend to the pre-epiglottic space in 20 (14%), extend to subglottis in 9(6%), extend to aryepiglottic fold, pharyngoepiglottic fold, or ventricular fold in 24(17%) patients. None of the patient requires tracheotomy during the surgery, but in 5 (3%) tracheostomy was necessary because of late post operative airway stenosis (1case), laryngeal oedema post radiotherapy (2cases), and postoperative aspiration with pneumonia (1case). For the neck management: 6% of the patient received radiation therapy, 42% neck dissection and 24% (33 patients) were included in a sentinel lymph node study protocol. From those 35 patients, 6 (17%) had micro metastasis in sentinel lymph node, and 29 (83%) were true NO. As for per or post operative complications, 120 (80%) had no complication, 10 (7%) present aspiration pneumonia, 6 (4%) postoperative bleeding stopped by electrocautery, the surgical margins was positive in 10 patients (7%), postoperative swallowing function showed a median value of 2 days for solid food, and 7days for liquid. The median hospital stay was 12days (1 : 49). Recurrent disease developed in 15patients (10%): 7patients (5%) developed local recurrence, 9 (6%) cervical recurrence, and 2(1,4%) local and cervical recurrences. In addition, 28patients (21%) developed a second primary tumour. The 5-year overall survival according to the Kaplan-Meier method was 70% + 5. There is no statistical correlation between overall survival, and tumour location, size, type of resection and neck dissection. The results of multivariable Cox proportional hazards model showed two parameters that were statistically significant, independent predictors of a reduced disease overall survival: cervical lymph node metastases (P = 0.040) and surgery centre (P = 0.022). Conclusions: Our result showed that the ELSL for the treatment of SC can achieved an excellent local and regional control of disease with a good laryngeal function. Therefore it should be considered as a valid option in the management of SC. Sentinel Node Biopsy can be successfully performed as a staging tool in early stage of SC.

S276: CLINICAL IMPACT OF INTRODUCING SUPRACRICOID LARYNGECTOMY WITH CHEP TO TREAT GLOTTIC CANCERS: EXPERIENCE ON 41 PATIENTS

Nakayama M, Seino Y, Hayashi S, Miyamoto S, Takeda M, Okamoto M, Nagahama, University School of Medicine, Sagamihara Kanagawa, Japan

Objective: Supraccricoid laryngectomy with Cricohyoidepiglottis-pxey (SCL-CHEP) is an organ preservation surgery indicated for early and selected advanced laryngeal cancers. To verify the clinical usefulness of SCL-CHEP, a retrospective comparative review was conducted at a university department. Methods: We summarized the clinical and postoperative data of 41 patients with glottic type squamous cell carcinoma who received SCL-CHEP over the past 10 years (1997-2007). Among the 41 patients, 18 were radiation failure cases and two had received 34 and 40 Gys of preoperative radiation therapy. Five-year survival rate of the SCL-CHEP patient group was compared with that of the patient group receiving TL (total laryngectomy) within the same period. Results: Wound infection was detected in 13 patients (32%). Those with severe infection, which required surgical intervention, included two cases of ruptured pexis and two cases of cysts because of cricoid cartilage necrosis induced by Forester disease. In post-SCL patient, because the remaining larynx was elevated by pexis, spurs at C3-4 seemed to be accountable for excessive physical contact and thus resulting in cricoid cartilage necrosis. Acceptable phonation, which is defined as the ability being able to communicate at the daily activities and social settings, was achieved by all patients with SCL-CHEP and most of the patients were able to resume work or enjoy their retirement lives. The average time required for completion of swallowing rehabilitation, excluding the six patients with prolonged status, was three weeks. Swallowing rehabilitation was done by ENT faculties and residents with assistance of speech pathologists, nurses, and dietitians. The final goal of swallowing rehabilitation was the ability to eat out and was achieved by 90% of the patients. The current data confirmed the reliable functional results of SCL. The 5-year overall survival rate, analyzed at the point of December 2005, was 86% for SCL group and 61% for the TL group (limited to Stage III and IV glottic cancer cases). Conclusions: In our opinion, SCL-CHEP can be indicated to be developed.

S277: TRANSORAL LASER MICROSURGERY FOR HYPOPHARYNGEAL CANCER

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Objective: To report the oncologic and functional outcomes of Transoral Laser Microsurgery (TLM) in the treatment of hypopharyngeal cancer. Methods: A prospective case-series analysis at 2 academic, tertiary referral centers. Thirty patients with pathologically confirmed squamous carcino-

moma of the hypopharynx treated with TLM between September 1996 and July 2007. Nineteen patients had previously untreated tumors. Seven patients had second primary tumors and 4 patients had recurrent primary tumors. TLM was completed in all 30 patients, neck dissection in 17 patients, adjuvant radiotherapy in 8 patients and adjuvant chemoradiotherapy in 1 patient. End points analyzed included, overall survival, disease-free survival, local control, locoregional control and distant metastases. Postoperative complications, duration of hospitalization and tracheotomy and feeding tube dependence were also examined. Results: The average follow-up period among surviving patients was 3.3 years. T stages and T stage estimates were: T1, 7 (23%); T2, 15 (50%); T3, 4 (13%) and T4, 4 (13%). Overall stages were stage I or II, 13 (43%) and stage III or IV, 17 (57%). Two-year disease-free overall survival rates were 63% and 64% respectively. Two-year local control and locoregional control rates were 84% and 69% respectively. The 5-year overall survival estimate was 53%. The average hospital stay was 3 days. Eighteen patients were alive and disease free at last follow-up. Two patients (11%) were gastrostomy dependent and 2 patients (11%) were tracheotomy dependent. No patient suffered a major complication following TLM. Six patients (20%) suffered minor complications: 4 patients with select primary or recurrent hypopharyngeal cancer, TLM with or without radiotherapy is a valid treatment strategy. Furthermore, low morbidity and mortality and excellent oncologic and functional outcomes make TLM an attractive therapeutic option.

S278: TREATMENT OF PHARYNGEAL CARCINOMAS BY LASER ENDOSCOPIC MICROSURGERY

Moreau P, Boucain O, Demez P, Moreau P, Liège, Belgium; University of Liège, Liège, Belgium

Objective: To determine the indications and to analyse the results of laser
endoscopic resection for pharyngeal cancers. **Methods:** A retrospective study of 74 patients operated from 1991 to 2005 for 82 pharyngeal cancers by CO2 laser microlyangyoscopic resection at University of Liége. 61 were previously untreated and 13 after failure of radiotherapy. 44 were localized in oropharynx (13 base of tongue, 15 lateral wall, 16 posterior wall) and 38 in hypopharynx (13 posterior wall, 25 pyriform sinus). Distribution of T for untreated lesions was: T1 12, T2 29, T3 27, T4 3. En bloc laryngectomy was performed in 12, 12 second laser procedure for histological margin involvement, 20 unilateral neck dissection, 10 bilateral, 20 postoperative radiotherapy. **Results:** The indications are small tumors, in one piece endoscopically resectable. For posterior wall, the tumors can be bigger, without other extension, with mobilization with respect to prevertebral area. Kaplan-Meier 5-year adjusted and overall survival rates are 91% and 49% respectively. The causes of deceases are 3 locoregional recurrences, 1 regional recurrence, 2 massive post-op bleedings, 1 aspiration. We have 7 local recurrences (9%) with 3 deceases, 3 laser recisions, 1 radiotherapy. Kaplan-Meier 10-year recurrence-free (laser cancer adjusted) survival rate is 85% for ENT, oesophageal, pulmonary cancers adjusted survival rate is 40%, and overall survival rate is 12, 18 patients (65%) in multiple cancers with 23 previous, 19 synchronous and 22 successive. The 74 patients add up to 175 cancers (154 ENT with 82 laser resections, 12 pulmonary, 9 oesophageal). **Conclusions:** CO2 laser resection for small pharyngeal cancers gives an excellent local control and adjusted survival. The main reason of decease is new other ENT, oesophageal or pulmonary cancers in relation to alcohol-tobacco. When possible, pharyngeal laser resection is preferable to radiotherapy to keep it for next carcinoma.

S279: PALLIATION OF RECURRENT HEAD AND NECK CARCINOMA WITH INTERSTITIAL PHOTODYNAMIC THERAPY. M.JH.Wijitjes1, S.de Vischer1, J.J.H.Roodenburg1, B.Tan2. 1University Medical Center, Groningen, The Netherlands; 2Netherlands Cancer Institute, Amsterdam, The Netherlands

**Objective:** Photodynamic Therapy (PDT) has proven to be effective in the palliation of incurable recurrences of head and neck squamous cell carcinoma. After injection with a photosensitizer, tumors are illuminated with incident light from a single fiber. In Foscan (mTHPC) based PDT tumors are illuminated with 652 nm light which results in a necrosis depth of approximately 10 mm. For treating larger tumor volumes the illumination can be performed with interstitially placed fibers. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Methods:** From 2005 -2007 eleven patients were treated with Foscan based PDT. The patients suffered from a recurrence of a squamous cell carcinoma (biopsy proven) and were either incurable or refused further treatment. Primary treatment involved concomitant radio-chemotherapy (n=7), surgery and radiotherapy (n=2) and radiotherapy (n=2). Tumor localization was base of tongue, floor of mouth, and oral tongue. A palliative regime was prescribed by the multidisciplinary H&N teams. Patients were injected with 0.15 mg/kg Foscan i.v., 96 hrs prior to illumination. In general anaesthesia a tracheotomy was performed. Hollow canules were placed in the tumor and surrounding the tumor. With plain X-ray films the positioning of the fibers was checked. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Methods:** From 2005 -2007 eleven patients were treated with Foscan based PDT. The patients suffered from a recurrence of a squamous cell carcinoma (biopsy proven) and were either incurable or refused further treatment. Primary treatment involved concomitant radio-chemotherapy (n=7), surgery and radiotherapy (n=2) and radiotherapy (n=2). Tumor localization was base of tongue, floor of mouth, and oral tongue. A palliative regime was prescribed by the multidisciplinary H&N teams. Patients were injected with 0.15 mg/kg Foscan i.v., 96 hrs prior to illumination. In general anaesthesia a tracheotomy was performed. Hollow canules were placed in the tumor and surrounding the tumor. With plain X-ray films the positioning of the fibers was checked. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Results:** Tumor response varied from 50-100 % established 8-12 weeks post-treatment by clinical evaluation or MRI. Four patients are alive with no evidence of disease 4, 12, 29, and 46 months after PDT. Four patients are alive with disease 4, 4, 4 and 9 months after PDT. Two patients died 4 and 19 months of their H&N tumor and one patient died of a lung carcinoma. **Conclusions:** Intestinal PDT seems to have potential for palliation in H&N squamous cell carcinoma. Remarkably, 4 patients seem to be cured from their recurrence after being diagnosed as incurable. A phase II study will be performed to evaluate the tumor response in a larger group of patients.

S280: PALLIATION OF RECURRENT HEAD AND NECK CARCINOMA WITH INTERSTITIAL PHOTODYNAMIC THERAPY. M.JH.Wijitjes1, S.de Vischer1, J.J.H.Roodenburg1, B.Tan2. 1University Medical Center, Groningen, The Netherlands; 2Netherlands Cancer Institute, Amsterdam, The Netherlands

**Objective:** Photodynamic Therapy (PDT) has proven to be effective in the palliation of incurable recurrences of head and neck squamous cell carcinoma. After injection with a photosensitizer, tumors are illuminated with incident light from a single fiber. In Foscan (mTHPC) based PDT tumors are illuminated with 652 nm light which results in a necrosis depth of approximately 10 mm. For treating larger tumor volumes the illumination can be performed with interstitially placed fibers. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Methods:** From 2005 -2007 eleven patients were treated with Foscan based PDT. The patients suffered from a recurrence of a squamous cell carcinoma (biopsy proven) and were either incurable or refused further treatment. Primary treatment involved concomitant radio-chemotherapy (n=7), surgery and radiotherapy (n=2) and radiotherapy (n=2). Tumor localization was base of tongue, floor of mouth, and oral tongue. A palliative regime was prescribed by the multidisciplinary H&N teams. Patients were injected with 0.15 mg/kg Foscan i.v., 96 hrs prior to illumination. In general anaesthesia a tracheotomy was performed. Hollow canules were placed in the tumor and surrounding the tumor. With plain X-ray films the positioning of the fibers was checked. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Methods:** From 2005 -2007 eleven patients were treated with Foscan based PDT. The patients suffered from a recurrence of a squamous cell carcinoma (biopsy proven) and were either incurable or refused further treatment. Primary treatment involved concomitant radio-chemotherapy (n=7), surgery and radiotherapy (n=2) and radiotherapy (n=2). Tumor localization was base of tongue, floor of mouth, and oral tongue. A palliative regime was prescribed by the multidisciplinary H&N teams. Patients were injected with 0.15 mg/kg Foscan i.v., 96 hrs prior to illumination. In general anaesthesia a tracheotomy was performed. Hollow canules were placed in the tumor and surrounding the tumor. With plain X-ray films the positioning of the fibers was checked. Here we describe our initial results of interstitial PDT with a palliative intent in recurrent H&N squamous cell carcinoma. **Results:** Tumor response varied from 50-100 % established 8-12 weeks post-treatment by clinical evaluation or MRI. Four patients are alive with no evidence of disease 4, 12, 29, and 46 months after PDT. Four patients are alive with disease 4, 4, 4 and 9 months after PDT. Two patients died 4 and 19 months of their H&N tumor and one patient died of a lung carcinoma. **Conclusions:** Intestinal PDT seems to have potential for palliation in H&N squamous cell carcinoma. Remarkably, 4 patients seem to be cured from their recurrence after being diagnosed as incurable. A phase II study will be performed to evaluate the tumor response in a larger group of patients.

S281: QUALITY OF LIFE AFTER NECK DISSECTION - JAPANESE MULTICENTER LONGITUDINAL STUDY. K.Nibi1, K.Kawabata2, T.Onitsuka3, T.Fujii4, M.Saikawa5. 1Kobe University, Kobe Japan; 2Cancer Institute Hospital, Tokyo, Japan; 3Shizuoka Cancer Center, Shizuoka, Japan; 4 Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; 5 National Cancer Center Hospital East, Chiba, Japan

**Objectives:** To assess the impact of rehabilitation and surgical modification, on the postoperative QOL, we performed a multicenter longitudinal study, using our neck dissection questionnaire (NDQ) and arm abduction test (AAT). **Methods:** Patients who had undergone neck dissection for the treatment of head and neck cancer answered NDQ and completed AAT, which were developed by “Study on Standardization of Treatment for Lymph Node Metastasis of Head and Neck Cancer, 1, 3, 6 and 12 months after the surgery. Items consisted of 1) stiffness of the neck, 2) constriction of the neck, 3) pain of the neck, 4) numbness of the neck, 5) shoulder drop, 6) shoulder stiffness and 7) neck appearance. Scores were assigned by rating response items from 1 to 5, with 5 representing better QOL and 1 representing worse. Patients were asked to abduct their arm with their palm down, and to rate the abduction from 0 to 5 according to the symptoms and objective measure of active shoulder range of motion. All patients enrolled in this trial had rehabilitation program designed for neck dissection. Obtained data were statistically analyzed according to the types of neck dissection and were also compared with those of the patients who had neck dissection but not had rehabilitation. **Results:** Two hundred and twenty four patients were enrolled in this study. Eight four patients underwent bilateral neck dissections and 140 patients underwent unilateral neck dissection for the treatment of head and neck cancers. Statistical analysis revealed resection of SCM, as well as SAN, led to shoulder drop. Shrinking the dissection levels and preservation of SAN and SCM did significantly reduce various sensory symptoms, such as, stiffness, pain, numbness and constriction as well as shoulder function. However, level IV dissection did not make significant difference in most items. Postoperative rehabilitation had significant effect on arm abduction ability, especially when SCM and/or SAN were resected. **Conclusions:** The study presented here demonstrated that rehabilitation in addition to modifications to radical neck dissection contribute to improve postoperative quality of life after neck dissection. Level IV dissection does not seem to have significant impact on postoperative QOL.

S282: SHOULDER MORAILITY AFTER SURGICAL AND NON-SURGICAL TREATMENT OF THE NECK. M.van Wouwe1, B.de Bree3, I.Verdonck1, D.Kuik1, C.de.Goede1, P.Doornaert1, C.Leemans1. 1VU University Medical Center, Amsterdam, The Netherlands

**Objectives:** The shoulder morbidity after surgical and non-surgical treat-
ment of the neck was determined, analyzed and compared. **Methods:** One hundred head and neck cancer patients who underwent treatment of the neck and visited the outpatient clinic for their regular follow-up visit, were included. One hundred seventy-four necks were treated by neck dissection alone (n=10), neck dissection and postoperative radiotherapy (n=41), radiotherapy alone (n=55) or chemoradiation (n=68). Neck dissections were radical (n=12), modified radical (n=26) and selective (n=13). Abduction (12.6%) and anteflexion (12.6%) were measured on both arms using an inclinometer. Endorotation and exorotation were scored on a 1-3 scale. Low shoulder position was scored. Subjective measurements were performed using the Visual Analogue Scale for pain and the Validated Shoulder Disability Questionnaire (SDQ). Subjective stiffness of the shoulder was scored. Statistical analyses (Kruskal-Wallis test, Mann-Whitney test, Chi-square test on logistic regression) were performed using SPSS 11.0.

**Results:** Fifty-four patients had some subjective complaints (SDQ score ≥ 2) and 52% of patients had no pathological evidence of disease in the dissection. Exorotation was better in the non-surgically treated group as compared to the surgically treated group (p<.01). The mean SDQ score was higher after neck dissection and radiotherapy than neck dissection alone (p<.01), but no difference between radiotherapy and chemoradiation was found (p=0.4). Stiffness and pain score were higher after surgical treatment as compared to non-surgical treatment (p<.01 and p<.01). For endorotation no difference after the different treatments was found (p=0.3). Exorotation was better in the non-surgically treated group than in the surgically treated group (p<.01). Anteflexion and abduction movements were better after non-surgical treatment than surgical treatment (p<.01). No differences between neck dissection and neck dissection with postoperative radiotherapy, and radiotherapy and chemoradiation were found for these movements. Radiation dose (< or > 50 Gy) and N-stage were not associated with increased morbidity. In the surgical treated group treatment of level V and sacrificing the spinal accessory nerve increased the morbidity. In the non-surgical group we found no significant correlation between treatment of level V and morbidity. **Conclusions:** Shoulder morbidity is present after non-surgical treatment of the neck, but to a lesser extent than after surgical treatment. It seems that chemotherapy does not add shoulder morbidity to radiotherapy.

**S283: DECREASED DISTANT METASTASIS AND IMPROVED SURVIVAL WITH NECK DISSECTION FOLLOWING CHEMORADIATION FOR N3 DISEASE**


**Objective:** To evaluate the role of neck dissection (ND) following chemoradiation (CRT) for advanced head and neck squamous cell carcinoma (HNSCC) with N3 disease. **Methods:** From March 1998 to September 2006, 584 patients with HNSCC were treated at Notre-Dame Hospital with concurrent CRT. Of these, 77 patients had N3 neck disease treated with CRT as primary therapy at diagnosis. The median age of the group was 54 years, 69% (89%) of whom were male and 8% (11%) female. The primary tumor site was the oropharynx in 56 (73%), unknown in 8 (10%), the nasopharynx in 7 (9.0%) and the remaining 6 (8%) were of the oral cavity (2.6%), the larynx (2.6%) or the hypopharynx (2.6%). Platinum based chemotherapy was administered to all patients. Radiation therapy was delivered by conventional technique in 83.5% and by IMRT in 16.5% with a median dose of 70 Gy. Response to treatment was assessed using clinical exam and CT-scan 6-8 weeks post treatment. Neck dissection was not routinely performed and considered for those with less than complete response. Thirty (39%) patients achieved clinical complete response (cCR) after CRT and, of these, two underwent ND as required by another study. Forty-seven (61%) patients achieved less than complete response and of these, 33 underwent ND (cPR-N). Survival and failure times were computed using Kaplan-Meier curves and compared with log rank tests. **Results:** Patients were followed for an estimated median time of 3.5 years. At last follow-up, 52% of cCR and 70% of cPR-N patients were alive. In the cPR-N group, 72% of patients had no pathological evidence of disease in the dissection specimen and 88% were considered free of disease after surgery. The cCR and cPR-N patients had a regional relapse rate of 9.7% and 3.0%, and distant relapse rate of 29% and 15%, respectively. When comparing the cCR and cPR-N groups at 2 years follow-up, the regional relapse free survival (RRFS) was respectively 89% and 96% (p=0.24), distant disease free survival (DDFS) was 66% and 93% (p=0.06), disease free survival (DFS) was 63% and 86% (p=0.055) and overall survival (OS) was 59% and 81% (p=0.17). **Conclusion:** In this single center retrospective analysis, patients with N3 disease who underwent neck dissection seemed to have a better outcome, regardless of response to CRT. These results suggest that neck dissection should be routinely offered to patients with N3 disease following CRT. Further confirmatory studies are warranted.

**S284: ULTRASOUND GUIDED ASPIRATION CYTOTOLOGY FOR THE ASSESSMENT OF THE CLINICALLY NON-NECK; FACTORS INFLUENCING ITS ACCURACY**

**M.W.van den Brekel**, **M. C. Borgemeester**, **F. A. Pameijer**, **M. F. van Velthuisjen**, **A. J. Balm**, **L. E. Smeele**, **1Netherlands Cancer Institute, Amsterdam, The Netherlands**

**Background:** Ultrasound guided-fine needle aspiration cytology (US-FNAC) can be used to diminish the risk of missing occult metastases and for early detection of recurrent neck disease during follow-up. It is popular in many countries in Europe and is gaining acceptance in the USA. It is routinely used in thyroid carcinoma as a diagnostic tool. In this retrospective study, US-guided fine needle aspiration biopsy was performed in 163 surgically treated patients with palpable neck nodes (ND). One hundred twenty six patients underwent a planned elective neck dissections (END), and 37 were planned for a wait and see (W&S) strategy but preoperative US-FNAC could change this policy if metastases were detected. In the W&S group mainly small oral cancers were included (T1 and superficial T2). US examinations were performed by different radiologists. For the W&S group the follow-up of the neck was the gold standard whereas for the END group the pathological findings in the ND specimen were used. **Results:** In the END group, US-FNAC had a sensitivity of 39%, which is quite low, but still comparable to many reports. However, in the W&S group, the sensitivity was only 18%. There was a large variation in sensitivities among radiologists. The incidence of occult metastases in the W&S group was almost 50%, which is very high. The five-year survival in the wait-and-see group did not differ from the patients with early oral cancer who underwent an END. **Discussion:** We are the first to report a difference in sensitivity of imaging between the W&S group and the END group. The patient population thus seems to play a role, apart from skill and motivation of the ultrasonographer. The reasons for this can be multiple. The most probable is that in the W&S group, in which the primary tumors are smaller, the lymph node metastases are also smaller and more easily missed at US-FNAC. The high incidence of occult metastases in the W&S group [higher than in the END group] might be due to the fact that histopathology overlooks these very small occult metastases and that the rate of these micrometastases is high in small primary tumors. Although the sensitivity of US-FNAC in this study is low, especially in small oral cancer, the prognosis in the wait-and-see group is not affected. However, from this study it appears that a wait-and-see strategy is only advantageous to a minority of the patients and very strict follow-up should be ensured. Submitted to Head & Neck.

**S285: INITIAL STAGING OF THE NECK IN HNSCC: IS PET/CT THE BEST?**

**S.J. Stocekli**, **T. Hany**, **B. Schuknecht**, **1University Hospital Zurich, Zurich, Switzerland**

**Objectives:** Traditionally, contrast enhanced high resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) have been used for the initial staging of head and neck squamous cell carcinomas (HNSCC). These modalities were also applied for staging of cervical lymph nodes. Many studies have shown that ultrasound (US) with fine needle aspiration cytology (FNAC) is very accurate in detecting lymph node metastases. In line postion emission tomography with 18-Fluoro-Deoxy-Glucose (FDG) and CT (PET/CT) combines morphologic and metabolic assessment of tumors. The aim of this study was to compare PET/CT to HRCT, MRI and US-FNAC with respect to neck staging prior to therapy. **Background:** Standard reference of the histologic work-up of the neck dissection specimen. **Methods:** All patients with a previously untreated HNSCC undergoing primary surgical therapy including neck dissection were eligible. Patients with prior treatment to the neck were excluded. The study was approved by the local Ethics committee, and patients were only included after written informed consent was obtained. All patients underwent HRCT, MRI, US-FNAC and PET/CT prior to neck dissection. Nodal staging as assessed by the different imaging modalities was compared to the standard.
of reference. Results: The total number of 78 consecutive patients have so far been prospectively included in the study. Conclusions: The patient accrual phase of this single-institution prospective study ends December, 31st 2007. The follow-up phase will end June, 30th 2008. As the study protocol does not allow interim data analysis the results will be presented at the 7th International Conference on Head and Neck Cancer in San Francisco in July 2008. The results of this study will show, which imaging modality will have the best accuracy to stage the neck in HNSCC.

S286: DW-MRI FOR NODAL STAGING OF LOCALLY ADVANCED HEAD AND NECK SQUMOUS CELL CARCINOMA: IMPACT ON RADIOTHERAPY PLANNING

2, V. Valentine2, 2P. DeLeris2, 1E. Verbelen2, R. Hermans2, 1University Hospitals Leuven, Leuven Belgium; 2University Hospitals Leuven, Leuven, Belgium

Objective: With highly conformal radiotherapy (RT) techniques, such as intensity-modulated radiotherapy (IMRT), accurate localization of head and neck squamous cell carcinoma (HNSCC) is crucial. This pilot study prospectively examined the use of diffusion-weighted (DW) magnetic resonance imaging (MRI) for nodal staging and its impact on RT planning. Methods: From June 2004 to April 2006, 22 patients with locally advanced HNSCC received a contrast-enhanced computed tomography (CT) as well as an MRI scan prior to neck dissection surgery. MRI examinations consisted of both routine turbo spin-echo (TSE) sequences and DW sequences with a large range of b-values (0 to 1000 sec/mm²). After topographic correlation, lymph nodes (LN) were evaluated microscopically with prekeratine-immunostaining. An optimal apparent diffusion coefficient (ADC) threshold for discriminating between malignant and benign LN was determined. A RT planning study was performed on these surgically treated patients. One set of target volumes was designed with conventional imaging (CT and TSE-MRI) guidance only, and another with the corresponding DW-MRI images. A third set was contoured solely based on pathology results and considered the gold standard. Results: Histopathological correlation was possible in 198 lymph nodes. Using an ADC threshold of 0.00094 mm²/sec, a sensitivity of 88.9% (40/45) and a specificity of 97.4% (149/153) per LN was found for DW-MRI. The neck level staging sensitivity and specificity for DW-MRI was 93.8% [30/32] and 96.9% [93/96], respectively. DW-MRI correctly detected nodal disease in 4 patients considered to have node-negative disease on conventional imaging and bilateral disease in 2 patients considered to have unilateral disease. Also, 2 patients considered to have nodal disease on conventional imaging were correctly downstaged to ND by DW-MRI. Nodal staging agreement between imaging results and pathology findings was significantly stronger for DW-MRI (Kappa 0.97; 95% confidence interval (CI): 0.84-1.00) than for conventional imaging (Kappa 0.56; 95% CI: 0.16-0.96; p = 0.03 by McNemar’s testing). For both imaging modalities, the absolute differences in RT volumes with those obtained by CT were calculated. Using the Dice similarity test, the observed difference was significantly larger for conventional imaging compared to DW-MRI for nodal gross tumor volume (p = 0.0013) as well as for nodal clinical target volume (p = 0.034) delineation. Indeed, the nodal clinical target volume (CTV) was correctly changed in 8 patients (increase in 6 patients and decrease in 2 patients). In 2 patients, the nodal CTV was underestimated based on DW-MRI; no underestimation of the target volumes occurred. Conclusions: These findings suggest that DW-MRI is superior to conventional imaging for pre-RT nodal staging of HNSCC, with an important potential impact on organ-sparing and disease control. Confirmatory trials should be initiated, preferably in comparison with fluoro-2-deoxyglucose (FDG) positron emission tomography (PET).

S287: DCE-MRI PERFUSION IMAGING OF HNSCC NODAL METASTASIS: IDENTIFYING RADIORESISTANCE AND THE DISTANT METASTATIC PHENOTYPE

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Nodal metastatic HNSCC (NM-HNSCC) represents a unique population of cells that have developed the metastatic phenotype which may or may not lead to distant metastasis. These cells may also have increased radioresistance which has lead to the practice of postradiotherapy neck dissections (ND). We hypothesized that an improved understanding of the microenvironment of NM-HNSCC will lead to improved patient selection and therapy. Methods: Since 2005, 50 subjects with NM-HNSCC (minimum 1 cm) treated with concurrent platinum based chemotherapy were prospectively enrolled and evaluated with DCE-MRI to evaluate the nodal perfusion. DCE-MRI was performed on a Siemens 1.5 or 3T scanner using a fast 3D spoiled gradient-echo sequence, modified to acquire eight angle-interleaved sub-aperture images from the full-echo radial data. This allowed for patient motion movement to be corrected for. A single dose of Gd-DTPA (0.1 mm/kg) was injected at 1 mL/s into an antecubital vein, followed by saline flush during which scanning was continued for another 9 minutes. The signal-intensity time curves from the first sixty seconds of the data from the near in tumor along with the arterial input function was used to compute the normalized integrated area under the curve (NIAUC60). This arbitrary parameter reflects the perfusion status of the tumor. Patients were treated in a uniform fashion utilizing a simultaneous inboost IMRT prescription technique to 70.4 Gy in 32 fr. Concurrent chemotherapy consisted of weekly carboplatin and paclitaxel or bolus cisplatin (100 mg/m²) in the majority of patients followed by a ND typically at 6-8 weeks. Follow-up interval was typically 1-3 months for the first 3 years. Descriptive statistics were used to summarize the data. Nonparametric statistical analysis was applied for comparative analyses. Results: 45 studies are available for analysis. Follow-up ranged from 1-21 months (mean 9 months). Preliminary analysis of the first 18 subjects with a minimum follow-up of 21 months demonstrated a significant correlation between low NIAUC60 and residual neck disease at ND or neck recurrence suggestive of radioresistance. Updated analysis of all 45 subjects available for analysis connotes to demonstrated a significant association between low nodal perfusion and radioresistance as defined (p=0.012). A significant association was seen between low nodal perfusion and the risk of distant metastasis (p=0.048). A scatterplot of nodal perfusion vs. nodal volume demonstrated an inverse relationship fitting a logarithmic model (R²=0.412, p<0.01). At the NIAUC60 cutoff of 0.4 which separated patients with residual neck disease / recurrence or no residual neck disease / recurrence, the logarithmic model predicted a corresponding nodal volume of 228 cc which reflects a nodal size of ~6x6x6 cm. Conclusions: These observations lead to speculations that poor pre-treatment tumour perfusion in the microenvironment may be a common mechanism associated with radioresistance and development of the distant metastatic phenotype. The prediction of a nodal size of ~6x6x6 cm corresponding to nodal perfusion which discriminated between those subjects with or without residual neck disease / recurrence provides internal validity for the clinical significance of nodal perfusion.

S288: POSITRON EMISSION TOMOGRAPHY IN THE MANAGEMENT OF HEAD AND NECK CANCER OF UNKNOWN PRIMARY

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Objective: Unknown primary squamous cell carcinomas of the head and neck (CUP) are primarily treated with radiation, frequently in combination with chemotherapy and/or neck dissection. Precise localization of the primary tumor will allow more focused radiation treatment to site of cancer and potentially result in reduced morbidity. Although the use of positron emission tomography (PET) for detection of occult primary cancer appears promising, there is still controversy regarding its value as a diagnostic tool in patients with CUP. In this study, we reviewed our experience with PET in patients with CUP and evaluated whether the use of PET scan changed our management of these patients. Methods: We performed a retrospective chart review of patients with biopsy proven squamous cell carcinoma of cervical lymph nodes with an unknown primary. PET was used as part of the diagnostic workup in 28 of these patients and they were included in this study. These patients also underwent a standard workup for CUP including CT scan and quadruple endoscopy with site directed biopsy of the nasopharynx, tonsil, base of tongue, and pyriform sinus. The rationale, timing, and results of the PET scan were documented. We identified any change in management of these patients based on results from the PET scan. Results: PET identified two possible occult primaries. These two patients were taken back to the OR for additional biopsies guided by the PET result. However, the biopsies were negative in both cases. Three patients with metastatic disease were correctly identified by both PET and CT scan. Conclusions: PET scan did not provide any additional information that was not obtained using the standard workup and biopsy. The only change in management occurred in two patients who were subjected to additional biopsies with no change in definitive therapy. We conclude that there is no benefit in the routine use of PET in patients with CUP, especially in centers with experienced head and neck surgeons and neuroradiologists.

CLINICAL: RECONSTRUCTION III

S289: FREE JEJUNUM VS. TUBED-FREE FLAPS FOR TOTAL
LARYNGOPHARYNGECTOMY DEFECTS: PATTERNS OF USE AND OUTCOMES

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Objectives: Review case series from two academic institutions performing total laryngopharyngectomy defect reconstructions with predominantly free jejunal or free-tubed flaps. Methods: A retrospective review of patient data from two different institutions from 1999 to 2007. Demographic data, indications for surgery, early and late post operative complications and swallowing outcomes were collected. Results: There were 36 jejunal free flaps (JFF) in 35 patients, and 22 tubed-free flaps (TFF) in 22 patients. The mean age of the JFF patients was 62 years (7-84), while the mean age of the TFF group was 64 years (47-79). The follow-up interval for the JFF group was 1 to 90 months (mean of 16 months), and for the TFF group the follow-up interval is 2 to 32 months (mean of 7 months). The TFF groups consisted of 15 radial forearm flaps, 4 anterolateral thigh flaps, and 3 rectus flaps. Indications for surgery in the JFF group included: primary squamous cell carcinoma (SCC) n=9, recurrent SCC n=15, thyroid carcinoma n=5, structure n=4, other n=2. In the TFF group, the indications for surgery were primary SCC n=8 and recurrent SCC n=14. There were 11 sternal resections and upper sternal resection in the JFF group, and 11 requiring a second free flap at time of surgery (radial forearm free flap) for neck skin coverage. None of the JFF patients required sternal resection, and 2 had a second free flap at time of surgery (pectoralis major). Mean hospital stay was significantly longer for the JFF patients 16 days compared to 9 days in the TFF patients (p=0.001). Flap survival was not significantly different in each of the groups (90% JFF; 95% TFF) (p=0.64). Early complications were present in 41% and 54% in the JFF and TFF groups, respectively. The most common early complication in both groups was fistula, 17% in JFF and 27% in TFF group (p=0.50). There were 3 in hospital deaths in the JFF group due to strokes and hemorrhage, all had undergone sternal resection. Late complications were present in 11% and 32% JFF and TFF flaps. The most common late complication in both groups was stricture, 6% in JFF and 23% in TFF patients (p=0.09). Swallowing results were statistically not different between the two groups. Speech rehabilitation was rarely performed in both groups. Conclusions: Jejunum free flaps and tube free-flaps are viable options for reconstruction of total laryngopharyngectomy defects. The JFF tended to be utilized for patients undergoing sternal resections with upper sternal resections. Longer hospital stays and more serious complications were associated with the JFF group especially those undergoing sternal resections.

S290: RADIAL FOREARM VERSUS ANTEROLATERAL THIGH FREE FLAPS FOR LARYNGOPHARYNGECTOMY DEFECTS: A RANDOMIZED TRIAL

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Objective: To investigate the use of anterolateral thigh flaps versus radial forearm free-flaps for the reconstruction of laryngopharyngectomy defects. Methods: Patients who were to undergo laryngopharyngectomy were randomized into either anterolateral thigh or radial forearm groups. The primary outcome measure was complication rate (flap failure, fistula formation, pharyngeal stenosis). Secondary outcome measures included donor site morbidity (cosmesis, limb function etc.). Results: There was a significant (p=0.04) increase in reconstructive complications in the anterolateral thigh group, including esophageal stenosis and pharyngeal fistulas. There was no significant difference in donor site complications. Conclusions: There is an increased free-flap complication rate without decreased flap donor site morbidity when using the anterolateral thigh flap to reconstruct laryngopharyngectomy defects. As such, we recommend the radial forearm free flap as the preferred flap for reconstruction of laryngopharyngectomy defects.

S291: PECTORALIS MYOFASCIAL FLAP REINFORCEMENT IN SALVAGE LARYNGECTOMY PREVENTS PHARYNGOCUTANEOUS FISTULA

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Objectives: Organ preservation protocols involving radiation with or without chemotherapy in the treatment of advanced laryngeal squamous cell carcinoma offers patients the prospect of preserving voice and swallow. Surgical treatment by total laryngectomy is then reserved for salvage situations involving either persistent or recurrent disease after chemoradiation therapy. As noted in several studies, the incidence of postoperative pharyngocutaneous fistula is significantly increased after salvage laryngectomy when compared to primary total laryngectomy. The purpose of this study is to determine if pectoralis myofascial flap reinforcement over primary pharyngeal closure during salvage laryngectomy can prevent postoperative pharyngocutaneous fistula. Methods: The head and neck tumor conference records at Stroger Hospital of Cook County were reviewed to identify all patients who underwent total laryngectomy from December 2003 until present. Only patients with resultant pharyngeal defects that could be closed primarily were included in the study, yielding a cohort of 32 patients. Medical charts were reviewed to extract data including demographics, clinical variables, use of pectoralis myofascial flap reinforcement, and presence or absence of post-operative complications with attention to pharyngocutaneous fistula. No patients receiving primary total laryngectomy received pectoralis flap reinforcement. For patients undergoing salvage laryngectomy, decision to perform pectoralis flap reinforcement was surgeon preference. In these cases, the pectoralis muscle flap was elevated while the pharynx was being closed to minimize operative time. Patients were then categorized according to type of closure used for salvage laryngectomy. Univariate analysis was performed to identify predictors of fistula in each of these groups. Results: Of the 32 patients, 19 were treated with primary total laryngectomy while 13 received salvage laryngectomy. Seven of 19 patients (37%) undergoing primary total laryngectomy developed pharyngocutaneous fistula. All patients in this group were closed primarily with no flap reinforcement. For salvage laryngectomy, three of six patients (50%) with primary pharyngeal closure developed pharyngocutaneous fistula; however, none of the seven patients undergoing salvage laryngectomy with pectoralis myofascial flap reinforcement developed pharyngocutaneous fistula. Chi square analysis of the association of mesh versus no mesh in patients undergoing salvage laryngectomy to be significant in regard to development of postoperative pharyngocutaneous fistula, with p < 0.05. Conclusions: The rate of pharyngocutaneous fistula with primary closure is 50% for salvage laryngectomy. The fistula rate drops to zero when a pectoralis myofascial flap is used to reinforce primary closure of the pharyngeal defect. The pectoralis myofascial flap during salvage laryngectomy is a simple and reliable technique that prevents post-operative pharyngocutaneous fistula and its associated morbidity.

S292: RADIAL FOREARM FREE FLAP FOR TOTAL LOWER LIP RECONSTRUCTION: THE ANALYSIS OF 10 CASES AND QUALITY OF LIFE EVALUATION

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Postresection defect of the total lip, especially when associated with soft tissues of lower face still remains a challenge for adequate reconstruction. Among many options microvascular free tissue transfer is the latest major advance and the main contributing factor in the quality of life improvement. The modern techniques are able to deliver well-vascularised tissues which allow to reconstruct even complex defects. The aim of lip restoration is to provide proper oral lining and external cheek skin and to reconstruct oral competence. There are several issues in lower lip reconstruction using microvascular tissues that must be considered, including defect’s size, aesthetic units, support, recreation of the vermilion and defects of associated tissues. Among many certain donor sites the radial myofascial flap (RFFF) has become a golden standard for majority of patients with total lip postresection defects. The aim of this paper is to present the group of 10 consecutive patients with lower lip cancer, where RFFF was used for functional lower lip reconstruction, with analysis of life. Quality. In the material the patient characteristics is presented with the details of RFFF modifications according to the type of lip suspension. Based on own QOL questionnaire, the functional and aesthetic results were analysed. The results suggest that the careful and detailed planning of the size, shape and type of lip suspension influence both functional and aesthetic results. Static lip suspension for defects limited to lower lip only is comparable to dynamic suspension in cases where the defect is complex and extended. Results of quality of life analysis may be a predictive factor influencing the choice of individual flap modification including the type of lip suspension.

S293: EFFICACY OF LOW MOLECULAR WEIGHT HEPARIN IN PREVENTING FREE FLAP FAILURE: A RAT MODEL

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Background: Free flap failures in reconstructive head and neck surgery is a significant cause of postoperative morbidity. Pharmacologic anticoagulation can lower this risk but the ideal medication remains to be found.
S294: LOW MOLECULAR WEIGHT HEPARIN THROMBOPROPHYLAXIS AND BLEEDING RISK IN HEAD AND NECK CANCER MICROVASCULAR RECONSTRUCTION

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Objective: A retrospective review of 66 cases of maxillectomy done during 2000 and 2007 using an angular artery tip of scapula flap for head and neck surgeons. Maxillary prostheses have long been the mainstay of reconstructive practice in maxillary reconstruction. Methods: A total of 60 Sprague-Dawley rats were randomized to the control or enoxaparin group. Each animal was administered saline or enoxaparin every 12 hours, starting two hours preoperatively. A fasciocutaneous free flap based on the femoral and superficial epigastric vessels was raised. The position of the flap was determined by the need to cover defects. A trend towards higher microvascular free flap failure in the host was observed in the high dose group - 4 complete (13%) and 1 partial failure) with bleeding complications. A trend to a higher free flap failure rate was observed in the high dose group - 4 complete (13%) and 1 partial failure) versus 1 complete (3%) and 1 partial failure in LG. There were no symptomatic thromboembolic events in either group, although there was one non-fatal pulmonary thromboembolism in one of the patients excluded due to non-adherence of the protocol. Conclusions: The increased dalteparin dose did not cause an apparent increase in conventional surgical bleeding complications – the null hypothesis was proven at evidence level 2b. However, a trend towards higher microvascular free flap failure was observed in the high dose group. A larger sample would be needed to explore any impact on both venous thromboembolic events and microvascular free flap failure rates.

S295: THE ANGULAR ARTERY TIP OF SCAPULA FREE FLAP: A NEW OPTION IN MAXILLARY RECONSTRUCTION

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Introduction: Reconstruction of maxillectomy defects remains a challenge for head and neck surgeons. Maxillary prostheses have long been the mainstays of treatment, but the challenge of the maxillectomy defect lacking structural elements to adequately support a prosthesis has led to use of free tissue transfer. This paper describes a novel reconstructive approach utilizing the angular artery tip of scapula flap in maxillary reconstruction. Methods: All patients in our prospectively maintained REB-approved free flap database in whom we used a angular artery tip of scapula flap were identified. Data was collected on patient comorbidities, extent of the ablative procedures, perioperative complications, and the following outcome measures: nature of oral diet, dental rehabilitation, flap complications, and shoulder function as evaluated by the DASH (Disability Assessment Shoulder-Hand) scale. Results: Between 2000 and 2007, 30 patients underwent maxillary reconstruction with the angular artery tip of scapular flap. The mean age was 65 years (range 40-79). There were five patients with cutaneous malignancies requiring maxillectomy and one with a sinonasal lesion; all other lesions originated in the oral cavity. The bone segment was used to reconstruct either the palate or the anterior face of the maxilla and orbital floor. Defect distribution, using the Okay classification, was as follows: Iiz-1, IIz-13, IIz-13, IIz-13. There were no flap failures; one patient underwent successful re-exploration for venous thrombosis. No patient required a vein graft for the vascular pedicle. There were no instances of perioperative donor site complications. There were four major medical complications, including pneumonia and cardiac arrhythmia. Mean hospital stay was 13.6 days (range 6-35). All patients resumed a full oral diet; no patient required a gastrostomy tube. Eight of the 30 patients have undergone comprehensive dental rehabilitation, two with adjunctive osseointegrated implants. There were two oroantral fistulas, both of which were amenable to closure with local rotation flaps. All patients regained normal donor site motion and function as evaluated by the DASH. Discussion: This study demonstrates that the angular artery tip of scapula flap offers a reliable and effective means of repairing complex defects of the midface and maxilla. This flap has the appropriate volume of bone and muscle to allow reconstruction of the most complex maxillary defects with the benefits of limited donor site morbidity and a long vascular pedicle.

S296: MAXILLECTOMY DEFECT RECONSTRUCTION OPTIONS AND OUTCOME

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Objective: Loss of mid-facial structures secondary to tumor extirpation has significant functional and aesthetic consequences. The variable loss of both soft tissue and/or bone leading to collapse of the lip, cheek, and per-oral soft tissues and palatal incompetence, present a challenging dilemma for reconstructive surgeons. The objective of this study was to evaluate the defects, reconstructive methods and the outcome in our patients and to develop a algorithm for planning reconstruction in these patients. Methods: A retrospective review of 66 cases of maxillectomy done during March 2004 to February 2007 (36 months). The system proposed by James Brown et al was used to classify maxillectomy defects. The vertical component was classified into Class 1, 2, and 3. Horizontal component in Class 2 and 3 corresponded to deviation of the maxillary alveolus from the side A, B and C. In addition data regarding the involvement of skin, skull base which has not been given due importance in the classification systems was collected. The reconstructive methods used in these patients were analysed. Patients with a minimum follow up period of 6 months were evaluated for the functional and aesthetic outcome. Functional assessment included speech, diet, trismus, nasal regurgitation and dental rehabilitation. Aesthetic results were assessed by the patient and the surgeon on a scale from excellent to poor. Results: 43(65%) were males and 23(35%) were females. 2A defect, the commonest was seen in 28(42%). Skin involvement was seen in 10(15%), skull base involvement in 8(12%). Free flaps were used for reconstruction in 42(64%) cases, double free flaps in 3 cases. Free radial forearm was the commonest free flap used; 30 patients who were alive and disease free with a minimum follow up of 6 were available for a functional and aesthetic assessment. Trismus was the functional problem identified in 14 cases (46%). 15(50%) patients were on soft diet. Aesthetic results were satisfactory. Conclusions: Maxillary and mid-face reconstruction is now possible with good reliability and predictability. Defect classification should include skin and skull base involvement. The algorithm developed by us base on this study could be used to plan reconstruction of maxillary defects.

S297: A PRACTICAL APPROACH TO MAXILLARY RECONSTRUCTION BASED UPON THE PATIENT'S DESIRE FOR DENTAL REHABILITATION

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Dental implant-supported prosthetic rehabilitation of patients with acquired maxillectomy defects who are reconstructed with bone-containing microvas-
cultural free flaps is challenged in the United States by a complex array of political, economic, social, and emotional factors. Objective: The purpose of this study is to evaluate a protocol that represents a practical approach to maxillary reconstruction in a consecutive series of head and neck cancer patients based on the patient’s desire for complete dental rehabilitation.

Methods: The records of 25 consecutive head and neck cancer patients that underwent various types of maxillectomy from 2004-2007 were retrospectively reviewed. Demographic variables were collected in addition to diagnosis, tumor site, stage, cancer therapy including radiation/chemotherapy and surgery, medical comorbidities, flap donor and recipient site, post-operative complications and flap survival. Prior to the planned surgical resection, all patients were given the option of a variety of reconstructive modalities, based upon the anatomy of the defect, the patient’s age and functional status, and the patient’s desire to undergo flap reconstruction.

Results: Eighty-four patients were evaluated regarding their satisfaction with reconstruction using the University of Washington Quality of Life questionnaire. Overall success rate of maxillary reconstruction was 93%. Minor complications, such as infection, hematoma, and wound dehiscence occurred in 24% of the patients. Only 12% of the patients completed dental implant-supported prosthetic rehabilitation. Of these, all implants successfully osseointegrated and patients were highly satisfied with their treatment, despite the added cost. All patients who were reconstructed with fasciocutaneous flaps or with non-implant supported osteocutaneous flaps were equally as pleased with their reconstruction. Conclusion: Few patients go on to complete implant-supported prosthetic rehabilitation. The current study suggests, however, that if patients are involved in an informed decision-making process, successful and functionally pleasing results can be achieved with a variety of techniques.

CLINICAL: THYROID IV

S298: POST-OPERATIVE COMPLICATIONS AFTER CENTRAL COMPARTMENT ELECTIVE LYMPH NODE EXCISION FOR PAPILLARY THYROID CANCER

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Objective: The role of elective central compartment lymph node dissection for papillary thyroid cancer remains controversial. The proponents justify performing it to potentially reduce recurrence. Opponents argue that the risk of a higher rate of post-operative complications including hypocalcemia and vocal cord paralysis outweighs its minimal impact on survival. Very few studies have actually compared complication rates between total thyroidectomy and/or avoid recurrent disease in the remaining lobe. This can be done safely and without any increase in morbidity.

Methods: The role of elective central compartment lymph node dissection was considered a complication because it was done intentionally. There was no permanent dental implant-supposed prosthetic rehabilitation. The current study suggests, however, that if patients are involved in an informed decision-making process, successful and functionally pleasing results can be achieved with a variety of techniques.

S299: COMPLICATIONS OF TOTAL THYROIDECTOMY IN BENIGN VS. MALIGNANT DISEASE

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Objective: Total thyroidectomy is the procedure of choice for many benign and malignant thyroid diseases. There is still controversy regarding the use of total versus subtotal thyroidectomy for benign disease because many surgeons fear it is associated with a high complication rate. To date, few studies have investigated the safety of total thyroidectomy in benign disease by directly comparing it to the complications of total thyroidectomy for malignant disease. Methods: A retrospective chart review of 411 consecutive patients undergoing total thyroidectomy performed by a single oncologic surgeon was analyzed to compare the complication rates in benign versus malignant disease. Serum ionized Ca and intactPTH levels were measured within one week postoperatively, and six months after operation. Permanent hypocalcemia and hypoparathyroidism were defined as an ionized calcium level below 1.10 mmol/L or an intact PTH of less than 14 pg/mL respectively, persisting longer than six months. Results: Of the 411 patients who underwent total thyroidectomy, 337 (82%) were female and 74 (18%) patients were male. Of these, 278 (68%) had benign pathology (group A) while the remaining 133 (32%) had malignant disease (group B). Benign pathologies included bilateral goiter (71%), Hashimoto’s thyroiditis (30%), follicular adenoma (10%), and benign (1%), where no pathology was identified (7%). There were no statistically significant differences noted (p<0.05) between the two groups. Among group B, four patients were noted to have permanent hypoparathyroidism, but two of these patients did not receive parathyroid reimplantation because of advanced malignant disease in the neck. The recurrent laryngeal nerve was sacrificed in five patients with direct nerve involvement, which was not considered a complication because it was done intentionally. There was no mortality in either group. Conclusion: The complication rates of total thyroideectomy appear to be equal between benign and malignant diseases, and in both cases, permanent complications are rare when performed by an experienced surgeon. Thereby, when performing total thyroidectomy in malignant and bilateral benign disease, one can avoid secondary complications of thyroidectomy and recurrent disease in the remaining lobe.

S300: UNILATERAL THYROID LOBECTOMY FOR DIFFERENTIATED THYROID CARCINOMA: A PROGNOSTIC INDEX (PI)

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Objective of the study: To evaluate the validity of unilateral thyroid lobectomy for patients (PTS) with unilateral differentiated thyroid carcinoma when prognostic factors are favourable (EORTC Prognostic Index (PI) inferior or equal to 50): local or regional recurrences (heterolateral lobe or neck lymph node) and survival. Material and Methods: Consecutive series of 577 PTS operated for differentiated thyroid cancers in our institution, from Jan. 1955 to dec. 2006, a total lobectomy (with isthmectomy) and/and their 8-year-old residing thyroid lobe (TL) in a cohort of patients in whom surgery was performed within the same time period consistently the same way by a single group of surgeons. Design: retrospective medical chart review. Setting: Academic tertiary center. Patients: Sixty eight patients with preoperative or intraoperative diagnosis of papillary thyroid cancer who underwent total thyroidectomy with elective or therapeutic central compartment lymph node dissection were compared to 73 patients who underwent total thyroidectomy without central compartment dissection for either benign (14) or indeterminate (59) disease. Thirty one (44%) of these 73 patients were ultimately found to have malignant disease on final pathology. The study period was between 07/2004 and 06/2006. Outcome Measures: Incidence of vocal cord paralysis, transient and permanent hypocalcemia (Ca<8.0). seroma, hematoma and chyle leak. Results: There were no patients (0%) with permanent hypocalcemia in either group. The incidence of transient hypocalcemia (Ca<8.0) in the CLND group was 17% (12 of 68) compared to 35% (22 of 73) in the TT group. Temporary vocal cord occurred in 5 of 68 (7.3%) patients in the CLND group vs. 6 of 73 (8%) in TT group. One (1.36%) patient in TT group had permanent VC paralysis. There was no permanent VC paralysis in the CLND group. There was no hematoma or seroma in either group. Conclusions: The complication rates of CLND were similar to that of TT alone in our series. Our results suggest that in the hands of experienced oncologic thyroid surgeons, it would be appropriate to perform elective central compartment dissection for PTC, at least in higher risk patients, to allow for more accurate staging and treatment, and potentially reduce the risks associated with reoperation.
specifc survival 100%. A 31 yrs patient developed, 7 yrs after thyroid lobectomy for a 1 cm papillary carcinoma, a pulmonary nodule on chest CT, positive by transbronchial biopsy and by PET scan. After contralateral thyroid lobectomy, she received one ablative dose of 131I, the whole body scan showed no uptake in the lung. She underwent a wedge pulmonary resection: papillary lung carcinoma (bronchioalveolar) with free margins. After uneventful recovery, discharged from hospital and she resumed to her daily activities. At the age of 25, she gave birth to two successive healthy babies. But she died 2 years later from disseminated lung cancer.

CONCLUSIONS: Unilateral lobectomy is justified for unilateral tumors (based on ultrasound) in patients of 18 yrs. This approach allowed us to perform an adequate lobectomy in 19% of cases and early second treatment she gave birth to two successive healthy babies. But she died 2 years later from disseminated lung cancer.

CONCLUSIONS: Unilateral lobectomy is justified for unilateral tumors (based on ultrasound) in patients of 18 yrs. This approach allowed us to perform an adequate lobectomy in 19% of cases and early second treatment she gave birth to two successive healthy babies. But she died 2 years later from disseminated lung cancer.

Objective: To determine a difference in recurrence and disease-related mortality between tall cell variant (TCV) papillary thyroid carcinoma compared to normal variant (NV) papillary thyroid cancer. Methods: A systematic literature search was conducted in MEDLINE, PubMed, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), and Google to identify articles published between January 1, 1980 and October 1, 2007. In addition bibliographic references of identified articles were searched for relevant articles. Studies comparing TCV to NV treated with total or subtotal thyroidectomy and a study population greater than or equal to 15 met inclusion criteria. Non-English published data and studies without recurrence or disease related mortality data for both TCV and NV were excluded. A total of 6 studies were reviewed. Both a fixed effects analysis and a random effects analysis were conducted on the recurrence and disease-related mortality data for all six studies generating an odds ratio and 95% confidence interval for each study. A Cochrane-Mantel-Haenszel method for both fixed and random effects determined the overall odds of recurrence of TCV compared to NV. An inverse-variance weighting for both fixed effects and random effects determined the overall odds of mortality for TCV compared to NV. Results: Summary odds ratios were 38.82 greater chance of mortality compared to normal variant thyroid carcinoma (PTC) who were less than 18 years of age at diagnosis. Study Design: Retrospective chart review of patients with PTC treated in referral cancer center. Patients and Methods: From 1993 to 2002, 1552 charts of thyroid carcinoma were reviewed. Twenty-nine patients (1.9%) had less than 18 years of age at diagnosis and had been treated primarily in our institution. Patient characteristics (age and gender), tumor factors (pathology, size of tumor, multifocality), type of treatment, recurrences and distant metastasis were analyzed using the chi-square method. The overall survival was estimated by the Kaplan-Meier method. The statistical analysis was performed using the SPSS software. Results: The papillary histological type was confirmed in all cases. The mean age was 12.21 years (range, 3-16 yrs), 22 patients were females and 7 were males. The mean time of symptoms was 15 months (range, 2-48). Eight patients (27.6%) had neck metastases at presentation. Total thyroidectomy was performed on 21 patients (72.4%); partial thyroidectomy was performed on 8 patients, post-operative radiodine therapy was administered to 21 patients (72.4%). Six patients (20.6%) developed regional recurrences and were salvaged by surgery; 4 (13.8%) patients developed distant metastases and were treated with radiodine therapy (RAI). The median time follow-up was 44 months (range, 12-120 months), and the median time for recurrence was 6 months (range, 2-54 months). Neck dissection was performed only in 8 N+ patients (27.6%). In the group of patients who underwent total thyroidectomy 5 patients (23.8%) had nodal recurrences, in comparison with 1 patient (12.5%) among those who underwent partial thyroidectomy (p = .67). Similarly, 28% of patients who received RAI developed distant metastases in comparison with 12.5% among those who did not (p = .65). No patient died from DTC. The 37.5% 5 yr DFS rate was lower in patients with lymph node metastases in comparison with the 95.2% rate found in patients without lymph node metastases. This result was statistically significant (log Rank 12.26, P = 0005). Conclusion: The presence of lymph node metastases was the only predictor of outcome of TCV patients. Our result found in our study suggests that the extent of surgical procedures of DTC in children should be tailored according to its clinical presentation.

S302: THE OUTCOME OF UNTREATED PAPILLARY THYROID CANCER CONFINED TO THE THYROID GLAND

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Objective: The incidence of thyroid cancer in the United States has more than doubled over the past 30 years, predominantly due to the increased detection of small papillary cancers. Autopsy studies show that there is a substantial reservoir of sub-clinical papillary thyroid cancer, so it is likely that this rising incidence reflects increased detection of sub-clinical disease that has always been present in the population, but not historically detected. The natural history of papillary thyroid cancer has not been systematically studied. Therefore, our objective is to describe the outcome of untreated papillary thyroid cancer. Methods: We analyzed data on 31,461 localized (e.g., no lymph node metastases) papillary thyroid cancer cases from the United States Surveillance, Epidemiology and End Results (SEER) program, which is managed by the National Cancer Institute. The main outcome measure was cancer-specific survival: the probability over time of surviving the cancer. Results: From 1973 to 2004, SEER recorded the cases of 372 people with localized papillary thyroid cancer who did not have surgery (the other 31,089 people did have surgery). The median age of the “no surgery” and “surgery” groups was 53 years and 46 years, respectively. The percentage of male patients in the “no surgery” and “surgery” groups was 30% and 19%, respectively. The 20 year cancer-specific survival of the “no surgery” group was 96%. Twenty year survival for the “surgery” group was only 2% better (98%) than the “no surgery” group. Since 1988, SEER has documented whether treatment for the cancer was recommended: among those patients who elected not to have surgery despite recommendations to do so, 10 year cancer-specific survival was 98% (95% CI: 95 – 100%). Conclusions: Localized papillary thyroid cancers have a very favorable survival outcome. This finding holds true even for patients for whom surgery was recommended but not done. Therefore, watchful waiting may be a viable alternative to immediate surgical management.
S304: PHASE II STUDY OF COMBRETASTATIN A4 PHOSPHATE (CA4P) IN PATIENTS WITH ADVANCED ANAPLASTIC THYROID CARCINOMA (ATC) E.Savvides1, C.J.Mooney1, M.M.Cooley1, S.S.Agawal2, A.Dowlati1, J.Wasman1, D.Wang1, J.Ortiz1, P.Layert1, S.Remick4, 1Case Comprehensive Cancer Center, Cleveland, OH; 2St Luke’s Hospital and Health Network, Bethlehem, PA; 3Karmanos Cancer Institute, Detroit, MI; 4Mary Babb Randolph Cancer Center, Morgantown, WV

Background: CA4P is the first tubulin-binding vascular disrupting agent (VDA) tested in the clinic, with demonstrable antitumor activity against anaplastic thyroid cancer (ATC) cell lines, xenografts, and demonstrable efficacy in a phase I trial. We now report the efficacy and safety results of the phase II trial. Methods: Patients with metastatic ATC, good performance status, normal ECG and cardiac function, and no prior therapy for disseminated disease were eligible for study. CA4P was administered as a 10-minute IV infusion on days 1, 8 and 15 every 28 days (1 cycle) until progression of disease. Baseline serum soluble intracellular adhesion molecule-1 (sICAM) levels were obtained at baseline, over the first 2 cycles and end of therapy. Results: Overall, CA4P was well tolerated. Grade 3 and 4 toxicities were observed in 9 patients (35%) and one (4%), respectively. QTc prolongation was seen in 4 patients causing one to stop treatment. Overall median survival was 47 months with 34% alive at 6 months and 23% at 12 months. Baseline serum soluble intracellular adhesion molecule-1 (sICAM) levels were measured in 24 of the 26 patients with a median of 253.5 ng/ml (range 172.0 – 839.5). There was a highly significant difference in event free survival in patients with lower baseline sICAM levels (p = 0.013). Conclusions: This is the largest prospective trial ever conducted for this rare disease. CA4P has an acceptable safety profile in the treatment of patients with advanced ATC. We were unable to demonstrate significant change in the natural history of ATC; one third of patients survived more than 6 months, which is encouraging. Despite a small sample size, low baseline sICAM levels were predictive of event free survival. Further prospective validation of sICAM as a therapeutic biomarker and exploring combination regimens with CA4P are warranted. [Supported in part by a clinical grant from OXiGENE, Inc., Waltham, MA and NIH grant nos. M01 RR-00080.]

S305: SUBSTERNAL GOITERS AND STERNOTOMY J.P.Cohen1, E.Mazzieri2, 1H&N Institute, Vassar Brothers Medical Center, Poughkeepsie, NY

Objective: To determine what factors predispose patients with substernal goiters to median sternotomy. Methods: Retrospective analysis of the author’s personal series of 113 substernal goiters operated upon during a 10 year time interval. Results: 108 goiters were successfully removed by a cervical approach. 4 patients required sternotomy, and it was concluded that one patient who did not receive sternotomy would have been better managed with sternotomy. Factors that influenced the need for sternotomy were massive size, malignancy, and the lack of a solid attachment between the substernal component of the thyroid to the gland in the neck. The latter was the most important factor. Revision surgery did not influence the need for enhanced surgical exposure. Conclusions: On the basis of appropriate preoperative imaging, it is possible to predict which patients with substernal goiters are likely to require median sternotomy. The most important factor was the lack of a solid attachment between the cervical and mediastinal components of the thyroid gland. Although previously reported, this factor has not received sufficient recognition in the management of substernal goiter.

S306: SURGICAL MANAGEMENT OF THYROID CARCINOMA: A SURVEY OF PRACTICE PATTERNS OF OTOLARYNGOLOGISTS AND GENERAL SURGEONS N.A.Herrera1, D.B.Villaret1, E.Mazzieri2, 1University of Florida, Department of Otolaryngology, Gainesville, FL; 2University of Florida, Department of Endocrinology, Gainesville, FL

Objective: To determine the differences in practice patterns of otolaryngologists and general surgeons in the surgical management of well-differentiated thyroid carcinoma. Materials and Methods: A fifteen question survey which focused on the surgical management of well-differentiated thyroid carcinoma was distributed to 7095 otolaryngologists and general surgeons in Florida, Georgia, Alabama, South Carolina, North Carolina, Mississippi, and Tennessee. 860 responses were returned representing a 12.1% response rate. The responses were catalogued and statistically analyzed using cumulative logistic regression and Chi-square/Fisher exact test. Results: There were statistically significant differences in the responses given by otolaryngologists compared to those given by general surgeons. Of the respondents, otolaryngologists report a higher frequency of performing thyroidectomies (p<.0001). Otolaryngologists report tumor histology rather than tumor size as the deciding factor for performing total thyroidectomy (p<.0001). Otolaryngologists are more likely to perform prophylactic level VI selective neck dissection (p<.0001). The responses as to which type of neck dissection should be performed in instances of proven cervical metastases from well-differentiated thyroid carcinoma differed significantly between otolaryngologists and general surgeons (p<.0001).

Conclusions: Our data suggest that there are statistically significant differences in the practice patterns of otolaryngologists and general surgeons in the surgical management of well-differentiated thyroid carcinoma. These differences may affect clinical outcomes in patients diagnosed and treated for well-differentiated thyroid carcinoma.

OUTCOMES: RADIATION ONCOLOGY-OTHER

S307: FUNCTIONAL OUTCOMES AND QUALITY OF LIFE ASSOCIATED WITH TWO TREATMENTS FOR PREVENTION OF RADIATION INDUCED XEROSTOMIA J.M.Rieger1, H.Seikaly1, N.Jho2, J.Harris1, D.Williams1, 1University of Alberta, Edmonton, AB, Canada; 2Cross Cancer Institute, Edmonton, AB, Canada

Objective: The objectives of this study were to: 1) assess functional outcomes in a longitudinal design in patients with head and neck cancer who were randomized to receive either a submandibular gland transfer (SGT) or pilocarpine during radiation as treatment for prevention of xerostomia, and 2) to relate objective assessments of speech and swallowing to salivary flow and quality of life (QOL). Methods: Only patients who had previously untreated and confirmed histological diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx or larynx. Patients with involvement of the oral tongue, maxilla, or nasopharynx were excluded. Patients received a radiation volume encompassing > or =80% of major salivary glands and had > or = 30 Gy delivered to that volume via external beam radiation. Between July 2004 and May 2007, 81 patients were referred for assessment of speech, swallowing and QOL at 4 predetermined times: 1) preoperative; 2) 1-mo postoperative; 3) 6-mo postoperative [post-RT]; and 4) 1-yr postoperative. Of these patients, 35 were randomized to the pilocarpine arm and 46 to the SGT arm. Outcome data also were collected for 37 patients who received neither the SGT nor pilocarpine. Functional Outcomes Assessment: Digitally-recorded speech stimuli for intelligibility and rate of words per minute were presented at baseline and at 4 predetermined time points. The results of this study will be reported only after that time.

S315: THE EFFECTS OF ROSENTAL GOITERS ON MEDICAL OUTCOMES: RADIATION ONCOLOGY-OTHER D.Normolle, PhD1, F.P.Worden, MD1, D.B.Chepeha, MD1, A.Eisbruch, MA, CCC-SP1, A.Sacco, BS1, F.Feng, MD1, S.S.Agarwala2, A.Dowlati1, J.Wasman1, D.Wang3, J.Ortiz1, P.Lavertu1, T.H.Lyden, MA, CCC-SP1, A.Sacco, BS1, F.Feng, MD1, D.Normolle, PhD1, F.P.Worden, MD1, D.B.Chepeha, MD1, A.Eisbruch, MA, CCC-SP1, A.Sacco, BS1, F.Feng, MD1, D.Normolle, PhD1, F.P.Worden, MD1, D.B.Chepeha, MD1, A.Eisbruch, MA, CCC-SP1, A.Sacco, BS1, F.Feng, MD1, D.Normolle, PhD1, F.P.Worden, MD1, D.B.Chepeha, MD1, A.Eisbruch, MA, CCC-SP1, A.Sacco, BS1, F.Feng, MD1, 1University of Michigan Health System, Ann Arbor, MI
To assess long-term swallowing function after chemo-IMRT between pre-therapy and 3 months after therapy. Multiagent concurrent chemotherapy and radiation represents an alternative to laryngectomy for patients with locally advanced squamous cell carcinoma of the larynx and hypopharynx. This approach produces significant acute toxicity and often results in late functional compromise. If tumor persists or recurs, patients still require a laryngectomy. This review of the Cleveland Clinic larynx preservation experience was conducted to identify patients most likely to benefit from this approach.

**Objectives:** To assess long-term swallowing function after chemo-IMRT which aimed to spare the swallowing structures. Methods: 57 patients with Stage III/IV cancer of the oropharynx (51) or nasopharynx (6) were treated with IMRT designed to spare the non-involved parotid glands, pharyngeal constrictors, and glottic/supraglottic larynx, concurrent with chemotherapy (oropharynx: weekly carboplatin 1 AUC and paclitaxel 30mg/m²; nasopharynx: cisplatin 100mg/m² q 2 weeks weekly). Objective: To determine whether videofluoroscopy (VF) (dysphagia larynx dysfunction) and observer-rated (RTOG pharyngeal/esophageal toxicity scores) assessments of swallowing function were undertaken before therapy and periodically through 2 years posttherapy. Results: Between pre-therapy and 3 months after therapy, statistically significant (p<0.05) worsening was observed in all VF parameters (except for pharyngeal transit times for liquids or solids, which did not worsen), in all patient-reported endpoints, and in observer-rated dysphagia. From 3 months through 2 years after therapy, almost all patient-reported items improved significantly (p<0.05) with many returning to baseline, and observer-based dysphagia assessment tended to improve (p=0.07). In comparison, no similar improvement was noted in the VF-based parameters, for which long-term swallowing, with occasional stasis, remained pure transit time worsened in long-term follow-up. Conclusions: Patient-reported dysphagia improved over time after the initial post-therapy worsening, however, no similar improvement was observed in most objective, VF items. This suggests that the swallowing mechanism of the patients compensates over time for the anatomical and functional changes caused by treatment, resulting in a lack of perception of dysphagia post-treatment. The lack of post-therapy improved with time changes from pre to post-therapy suggests a measurable benefit of the sparing of the swallowing structures by IMRT.

**Objective:** Clinical predictors of survival with a functional larynx after multiagent concurrent chemotherapy and radiation. Methods: Pre-1989-2006, 115 patients with locoregionally advanced squamous cell carcinoma of the larynx and hypopharynx were treated with four day continuous intravenous infusions of cisplatin (20mg/m²/day) and fluorouracil (1000mg/m²/day) during the first and fourth week of a definitive course of once or twice daily radiation. Laryngectomy was reserved for locally persistent or recurrent disease. Survival with a functional larynx was defined by the events of death from any cause, local recurrence, laryngectomy and permanent feeding tube or tracheotomy dependence. Results: The median age of this patient cohort was 59 (range 31-77) years; 87 patients (76%) were male and 102(89%) were Caucasian. The primary site was in the larynx in 46 patients (40%), supraglottis in 50(43%) and glottis in 19(17%). Tumor was T1 in 4 patients(3%), T2 in 31(27%), T3 in 42(37%), T4 in 37(32%), and TX in 1(1%). Disease was stage II in 8 patients (7%), III in 34(30%), and IV in 73(63%). Eastern Cooperative Oncology Group performance status (PS) was 0 in 57 patients(50%), 1 in 56(49%) and >1 in 22%. With a median follow up of 62 (range 5-195) months, the 5-year Kaplan-Meier projected survival with a functional larynx was 49%. No clinical characteristics including patient demographics, tumor stage, differentiation, primary site, hemoglobin, smoking or radiation fraction proved predictive of this outcome. Other projected outcomes at 5 years included an overall survival of 58%, survival with larynx preservation 52%, local control without surgery 82% and local control (including surgical salvage) 94%. Compared to PS 0, survival without surgery was superior in patients with PS 0 vs. 1 (91% vs.72%, p=0.007) and T1 vs. T3-4 disease (97% vs. 75%, p=0.01). Surgical salvage proved successful in 13 of the 19 patients (68%) with either primary site persistence (5 patients), local recurrence (14 patients) or chemo radiation therapy. Conclusions: Survival with a functional larynx could not be predicted by tumor and patient characteristics, with all patient subsets having equally good outcomes. Although local failure was more likely in patients with PS=0 and T3-4 disease, it was infrequent and could be effectively managed with surgical salvage.

**Objective:** The multi-disciplinary team (MDT) working with head and neck cancer (H&NC) typically draw upon research, their experiences and clinical insight when formulating a clinical treatment plan. The aim of this study was to investigate whether members of the MDT within the same profession had similar judgements, and whether these differed from other professional groups when predicting the quality of life (QOL) for a patient pre-treatment. Methods: A convenience sample of professionals working within the MDT read a description of a fictitious patient. Respondents recorded their predictions on a visual analogue scale with reference to symptoms and psychosocial difficulties based on a thematic review of the literature, and involving the European Organisation for Research and Treatment of Cancer core and disease specific questionnaires. Results: One way between groups analyses of variance were conducted to explore whether sub-groups of the MDT (nurses, doctors and all other MDT members) differed in their attributions on any of the 20 variables. Significant results were found, for worry and depression such that nurses are more likely than other MDT members to ascribe worry and depression to patients, irrespective of tumour size. In absolute terms, all respondents tended to attribute high degrees of worry, anxiety and allied problems to the hypothetical patient, irrespective of the size of the presenting tumour. Conclusions: Despite having different emphasis on training, different professional groups have very similar responses to the quality of life for an oral cancer patient. It is conceivable that MDT members consider the cancer itself to be the main driver of their predictions. The assumption of high levels of patient anxiety may also impact on the behaviour of both the MDT and the patient, and the dynamic interaction between them; this is particularly a problem with H&NC, which has a poor prognosis, high recurrence and mortality figure. Consequently, the behaviours the team exhibit, and the language they use may well be negative, or cautious irrespective of the patient’s actual psychological state. This accords with a review of MDTs’ perceptions of caring for cancer patients generally which suggested that MDT members tended to ascribe high levels of anxiety and distress to all patients with a cancer diagnosis, and to overestimate patient distress and under-estimate QOL. In practice this is an area that postgraduate education and training of MDT members should address, particularly those receiving MDT training. When interdisciplinary teams who have a more negative interpretation of their disease than the patients themselves. The study highlights the need for members of the MDT to communicate directly with the patient and receive their cues from them with reference to their needs and emotional status rather than predicting from their experience of previous cases/loads that the patient will be receiving or have a greatly reduced QOL as a result of their disease and recent
S312: PREDICTORS OF OUTCOME FOR ADVANCED STAGE SUPRAGLOTTIC LARYNGEAL CANCER

The necessity of panendoscopy for head and neck cancer patients with advanced stage supraglottic laryngeal carcinoma and to identify patient and tumor related factors predicting outcome.

Materials and Methods: 181 patients with advanced stage (stage III/IV) supraglottic carcinoma of the larynx were identified from a pre-existing database of 662 patients with squamous cell carcinoma of the larynx treated at Memorial Sloan-Kettering Cancer Center between the years 1984 and 1998. Sixty nine (38%) patients were treated by surgery + postoperative radiotherapy (S + PORT), 93 (52%) by chemoradiotherapy (CRT) and 19 (10%) by radiotherapy alone (RT). Disease specific survival (DSS), overall survival (OS), local recurrence free survival (LRS), regional recurrence free survival (RRFS) and distant recurrence free survival (DRFS) were calculated using the Kaplan-Meier method. Predictors of outcome were identified using multivariate analysis. Results: With a median follow up of 56 months, the 3 year OS and DSS for all patients was 53% and 71% respectively. The main independent predictors of OS and DSS were age greater than 60 years and stage of the neck at presentation. Patients over 60 years of age were 3 times more likely to die of disease compared to patients less than 60 years of age. Patients with clinical N2/N3 neck disease at presentation were 2.4 times more likely to die of disease and 2.5 times more likely to develop metastatic disease compared to patients with a clinically negative neck (N0) at presentation.

Conclusion: Regardless of index treatment, age over 60 years and clinical stage of the neck at presentation were the main independent predictors of OS and DSS for advanced stage supraglottic carcinoma by multivariate analysis.

S313: IF CONCOMITANT-BOOST RT IS USED FOR PATIENTS WITH HEAD AND NECK CANCER THE WEEKEND BREAKS HAVE NOT WORSENED THE OUTCOME

Objective: To evaluate if adding a weekend break to rapid accelerated hypofractionated radiotherapy will have an effect on the outcome in patients with advanced head and neck cancer.

Methods: 23 sequential patients with SCC of oral cavity, oro- and hypopharynx and supraglottic larynx in stage T2-4N0-1M0 were randomized between two definitive radiotherapy treatments: continuous accelerated irradiation (CAIR) - 7 fractions in 7-days-a-week and accelerated radiotherapy with concomitant boost (AR-CB) - 7 fractions in 5-days-a-week. Patients have been stratified per tumor site (larynx 48%, oropharynx 34%, oral cavity 9%, hypopharynx 9%) and stage (T2N0 31%, T2N1 10%, T3N0 29%, T3N1 13%, T4N0 12%, T4N1 12%). Fractionation parameters and radiation technique were the same in both arms: 1.8 Gy of dose per fraction, total dose and overall treatment time respectively in range 66.6-72.7 Gy and 37-40 days (depending on stage); all treatments were planned in 3D-Conservative technique, where CTV should received 54 Gy in 30 fractions and GTV - primary tumor and involved node - additional 12.6-18 Gy in 7-10 fractions. The only differences between arms has come from the timing of fractionation: in CAIR arm 1.8 Gy is given once-a-day at 24 hour interval, 7 days a week including Saturdays and Sundays, in AR-CB arm 1.8 Gy is given once-a-day on Mondays, Wednesdays and Thursdays, whereas at Tuesdays and Fridays twice-a-day with 8 hour interval. Results: Median follow-up is 70 months. Number of compliance patients is as high as 325 (94%). For all trial endpoints similar rates in CAIR and in AR-CB arms are noted. Confluent mucositis was the main acute toxicity with the incidence of 89% in CAIR patients and 86% in AR-CB. Actuarial 5 Year Grade 3-4 Morbidity-Free survival rate is 95% for both treatments. Local Control at 5 years is 67% in the CAIR and 68% in AR-CB arm. Disease-Free Survival and Overall Survival rates are respectively 38% vs. 44% and 50% vs. 55% and come of, among others, the second primary tumors (38 patients) and the distant metastases (11 patients). Conclusions: For moderately advanced head and neck cancer patients accelerated radiotherapy using 7 fractions a week of 1.8 Gy could be worthy of use effective treatment irrespective of the radiation is delivered over the weekend or not. Almost identical toxicity and tumor-cure profiles suggest the same biological effectiveness. Hence is a strong assumption that during accelerated radiotherapy with no compromise of total dose the weekend breaks are unimportant.

S314: COMPLICATIONS AND FINDINGS IN PANENDOSCOPY OF CHEMORADIATED PATIENTS

Objective: The necessity of panendoscopy for head and neck cancer patients is controversial in an era of high resolution computed tomographic (CT) scanning and other non-operative testing. Little data exists regarding panendoscopy in post-chemoradiation patients.

Methods: Retrospective Review of 80 patients with advanced head and neck cancer who underwent panendoscopy prior and post radiation or chemo radiation therapy and aerodigestive tract surveillance. Results: Pre-treatment bronchoscopy revealed one endobronchial lesion that was not detected by CT. There were no pre-treatment esophageal lesions. Suspicious lung lesions were identified in 14 post-treatment patients (18%), 4 of whom were ultimately found to have metastatic disease. However, post-treatment bronchoscopy did not add additional diagnostic information to that provided by CT. Post-treatment esophagoscopy was utilized for both diagnosis and treatment of 26 strictures and webs (33%), but no malignant esophageal lesions were found. Eighteen of these 26 abnormalities (69%) were detected on oesophageal motility study prior to esophagoscopy. There were 4 pre-treatment panendoscopy complications (5%): 1 minor pharyngoesophageal laceration, 3 minor airway complications, and 1 major airway complication (urgent post-procedure tracheotomy). Post-treatment panendoscopy resulted in 12 minor complications (15%): 3 patients with transient airway obstruction and 8 patients with pharyngoesophageal lacerations, but no major complications (e.g. surgical airway, esophageal perforation, or major bleeding). Six of the 8 post-treatment pharyngoesophageal complications, and 2 of the 3 airway complications were in patients with strictures or webs. Therefore, 8 of the 26 patients (30%) with esophageal abnormalities experienced complications, compared to 3 of the 54 patients without esophageal abnormalities (6%, p=0.004). Six of the 24 patients (25%) with laryngeal primaries had complications, compared to 5 of the 56 patients (9%, p=0.078) with other primary sites. Conclusions: Full panendoscopy in post-chemoradia tion head and neck cancer patients is relatively safe but may not add much to a simple evaluation of the primary site beyond diagnosis and treatment of esophageal stricture. Patients with esophageal abnormalities and laryngeal primary have a higher incidence of complications. Less invasive screening of the upper aerodigestive tract may be an appropriate option for most patients.

S315: RANDOM POSITIONAL VARIATION AMONGST THE SKULL, MANDIBLE AND CERVICAL SPINE IN DAILY SETUP FOR HEAD AND NECK RADIO THERAPY

Objective: Intensity Modulated Radiation Therapy (IMRT) can reduce acute and late toxicity without compromising tumor coverage in patients receiving radiation therapy for head and neck cancer. However, this assumes finite and predictable variations in patient position as a patient undergoes a 6-7 week course of radiotherapy. With over 48 degrees of freedom in movement from the skull to C7, we seek to quantify the extent to which the skull and components of the cervical spine may move in relation with each other between radiotherapy sessions.

Methods: 23 sequential head and neck radiotherapy patients with loco-regionally advanced disease underwent prospective, serial planning scans on a dedicated kilovoltage CT scanner. All patients were immobilized with a short face thermoplastic mask custom-fitted to the contours of patient’s face and head. This setup was reproduced during daily radiotherapy, as well as during planned rescans on the original CT scanner at approximately 11, 22 and 33 fractions for a total of 93 scans. The midpoint of the base of the dens was taken as reference for the position of the multiple foramina of the skull, mandible,
Following 24 hours of incubation, curcumin was found to inhibit HNSCC cell lines. TSA, LBH589 or MGCD0103 was determined by sulforhodamine B (SRB) irradiation. Sensitivity of selected cell lines to radiotherapy +/- DAC +/- MGCD0103 resulted in 75-90% and 86-99% survival, respectively. The incubation with 10nM TSA reduced survival to 51-98% of the control levels after 24h of acetylation status of histones H3 and H4. For the HDAC-I, a dose of 100nM TSA resulted in a dose-dependent upregulation of expression and EGFR phosphorylation.

**Basics and translation movement of the skull and the lower cervical spine.** No correlation was found between change in position and fraction number. The random, semi-rigid variations in positioning of the skull and spine point to a need for improved methods of immobilization and confirmation of patient positioning for radiotherapy of the head and neck.

**Introduction:** Promoter hypermethylation and histone deacetylation are the major epigenetic changes identified in cancer. Of major interest is the reversibility of these processes, which has led to the implementation of several new drugs in cancer therapy. Histone deacetylase inhibitors (HDAC-I) have radiosensitizing effects in several cancer types. The aim of this project was to explore if the HDAC-I TrichostatinA (TSA), LBH589 (Novartis) and MGCD0103 (Methylenex) act as radiosensitizers in head and neck squamous cell carcinoma (HNSCC) cell lines. Furthermore, the radiosensitizing potential of the demethylating agent Decitabine (DAC), either alone or in combination with HDAC-I, was determined.**Material and methods:** Methylation-specific PCR (MSP) was used to assess hypermethylation of 21 target genes in 9 HNSCC cell lines. The target genes included both genes known to be epigenetically silenced in head and neck cancer as well as new candidate genes that were selected by an in silico algorithm and involved in the normal molecular response to ionizing radiation. Sensitivity of selected cell lines to radiotherapy was determined by sulforhodamine B (SRB) assay. The effect on cellular proliferation was evaluated by BrdU assays. Treatment with HDAC-I for 24h resulted in a dose-dependent upregulation of acetylation status of histones H3 and H4. For the HDAC-I, a dose of 100nM TSA reduced survival to 51-98% of the control levels after 24h incubation. Likewise, an incubation with 10nM LBH589 and 500nM MGCD0103 resulted in 75-90% and 86-99% survival, respectively. The incubation with 10nM LBH589 and 500nM MGCD0103 was determined by sulforhodamine B (SRB) assay. The effect on cellular proliferation was evaluated by BrdU assays. Results: While a cell line-dependent substantial methylation was seen for the known genes, only one candidate gene (PARP3) was methylated in only one cell line. After treatment with DAC + HDAC-I, protein expression of epigenetically silenced genes was upregulated. Treatment with HDAC-I for 24h resulted in a dose-dependent upregulation of acetylation status of histones H3 and H4. For the HDAC-I, a dose of 100nM TSA reduced survival to 51-98% of the control levels after 24h incubation. Likewise, an incubation with 10nM LBH589 and 500nM MGCD0103 resulted in 75-90% and 86-99% survival, respectively. The same doses of HDA-I exerted a significant effect on cellular proliferation, respectively 0.22%, 15.28% and 70.3-100% of the control levels. HDAC inhibition alone did not result in clear radiosensitizing effects at the administered doses. Decitabine alone or in combination with HDAC-I showed some radiosensitization, the most promising combination being DAC+MGCD0103. Conclusions: A radiosensitizing effect of the demethylating drug DAC was found in HNSCC cell lines following incubation with a molar effective dose of 48h. A combination of DAC with HDAC-I seemed to result in enhanced radiosensitization. The underlying working mechanisms of these effects are currently explored.
Background: There is a need for chemopreventive agents in preventing second primaries and recurrences in HNSCC. A natural product isolated from turmeric, curcumin (available as Curcumin C3 Complex®) is currently undergoing clinical trials for colon, skin, pancreatic, and hematologic cancers, although its effect on oral HNSCC is limited due to low gastrointestinal absorption. In addition to NF3B pathway inhibition, studies in rabbit models have shown curcumin potentially inhibits the mTOR pathway contributing to its anti-tumorigenic effects. Studies have shown increased bioavailability of curcumin when administered with the black pepper extract Bioperine®, but this is controversial. Our in vitro data with a variety of HNSCC cell lines using the MTT assay has consistently demonstrated extreme sensitivity of HNSCC cell lines to curcumin with cytostasis at 5 38CM and cytotoxicity at 1038CM curcumin. These effects led us to explore the role curcumin plays in established tumors in a HNSCC cell line.

Objective: To determine whether curcumin has growth inhibitory effects in HNSCC in an in vivo model and determine whether Bioperine® could enhance the growth inhibitory effects of curcumin in nude mice. Methods: Balb/c nu/nu mice were injected subcutaneously with 1 x 106 SCC40 cells in each flank (Dr. Susan Gollin, Pittsburgh). When tumors reached 0B8 40mm3 animals were randomized into 3 groups of 8-9 mice each and treated with daily gavage of vehicle or 5 mg Curcumin C3 Complex® with or without Bioperine® for 3 weeks. Average differences in tumor volumes were compared between the 3 treatment groups. Harvested tumors were snap-frozen for protein analysis or formalin fixed for IHC staining. Results: Curcumin inhibited growth during the period of drug administration compared to control. There was no significant difference in tumor volumes between mice receiving Curcumin C3 Complex® with or without Bioperine® which is supposed to improve bioavailability. There was a significant difference (p=0.02) in average tumor volumes between control and both treatment groups for the early time points when tumors were of smaller volumes, although there was no significant difference in tumor volumes between control and treated groups for the late time points (p=0.55). Using the Wilcoxon Rank Sum (WRS) test, there was a significant difference (p=0.03) between the early and late phase average differences between control and treatment mice. To determine potential biomarkers of intermediate end points for chemopreventive studies with curcumin we measured markers downstream of the mTOR pathway and found that curcumin inhibited the mTOR pathway in tumors that were analyzed. Conclusions: Curcumin has growth inhibitory effects in HNSCC in vivo. There was no significant difference in growth inhibition when Bioperine® was added. The growth inhibitory effects were noted in the early time points when tumors were smaller in size compared to its effects when tumors were already larger as expected with a chemopreventive agent as its role is as a chemopreventive agent rather than a therapeutic agent. Although molecular targets of curcumin have not been well established preliminary results show that targets downstream of mTOR could potentially be biomarkers for curcumin chemoprevention studies.

S320: REAL TIME, IN VIVO SAMPLING AND ANALYSIS OF THE MICROENVIRONMENT OF ORAL SQUAMOUS CELL CARCINOMA L. Schmidt1, M. Hardt1,1 University of California San Francisco, San Francisco, CA

Introduction: The optimal cancer biomarker provides accurate information reflecting a cancer’s behavior in its host environment and can be readily detectable by non-invasive means. Progress towards such a biomarker has been impeded by the expansive profile of proteins and peptides produced by the cancer which are not a consequence of carcinogenesis and are products of normal cellular metabolism. In this study we have devised a novel strategy using in vivo microdialysis in patients for directly sampling the tumor microenvironment to collect and identify peptides which are the products of reactions catalyzed by proteinases secreted by the carcinoma.

Methods: Extracellular proteins and peptides from the local surrounding of an oral carcinoma were collected throughout neck dissections (typically 4-5 hours) via microdialysis probes (30 kDa MW cutoff). Anatomically matched, unaffected sites were simultaneously probed, and 1h-fractions were stored in a refrigerated fraction collector until transfer into -80°C storage. Samples were analyzed using a mass-spectrometry based assay, PALEO (proteinase activity labeling employing 18O-enriched water) that we have recently developed. This novel assay demonstrates and characterizes cancer specific proteolytic activity, including the proteolysis of peptides in the microsampling collection. Results: We collected microdialysis samples from the oral squamous cell carcinoma microenvironment in eight oral cancer patients. In each of these samples we detected peptides and proteins. PALEO-assessment of the samples showed that active proteolytic processing was still occurring in these samples, and we monitored the peptide generation by ex vivo incubation of the samples. Mass spectrometry-based peptide identification allowed us to identify protein substrates and peptide products for these proteolytic processes. Conclusions: Microdialysis hyphenated with our newly developed mass spectrometry-based proteolytic profiling methodology allowed us to track the dynamic interplay between oral squamous cell carcinomas and their surrounding environment in terms of proteinases and bioactive peptides. This study demonstrates that our novel in vivo microdialysis approach combined with a targeted proteomics approach is a very promising strategy to discover cancer biomarkers.

S321: GALANIN RECEPTOR 2 SUPPRESSES CELL PROLIFERA- TION AND INDUCES APOPTOSIS IN P53 MUTANT HEAD AND NECK CANCER CELLS K. Kanazawa1, P. Komarejczyk2, B. Kuman2, K. Misawa2, Y. Misawa2, I. Jang3, T. Ilino1, T. E. Carey4, I. Jichi Medical University Saitama Medical Center, Saitama City Japan; 2The University of Michigan, Ann Arbor, MI

Introduction: Galanin and its receptors are potential therapeutic targets for cancer therapy but their function in cancer is poorly understood. We therefore investigated the role of GALR2 signaling downstream of the mTOR pathway and found that curcumin inhibited growth during the period of drug administration compared to control. There was no significant difference in tumor volumes between mice receiving Curcumin C3 Complex® with or without Bioperine® which is supposed to improve bioavailability. There was a significant difference (p=0.02) in average tumor volumes between control and both treatment groups for the early time points when tumors were of smaller volumes, although there was no significant difference in tumor volumes between control and treated groups for the late time points (p=0.55). Using the Wilcoxon Rank Sum (WRS) test, there was a significant difference (p=0.03) between the early and late phase average differences between control and treatment mice. To determine potential biomarkers of intermediate end points for chemopreventive studies with curcumin we measured markers downstream of the mTOR pathway and found that curcumin inhibited the mTOR pathway in tumors that were analyzed. Conclusions: Curcumin has growth inhibitory effects in HNSCC in vivo. There was no significant difference in growth inhibition when Bioperine® was added. The growth inhibitory effects were noted in the early time points when tumors were smaller in size compared to its effects when tumors were already larger as expected with a chemopreventive agent as its role is as a chemopreventive agent rather than a therapeutic agent. Although molecular targets of curcumin have not been well established preliminary results show that targets downstream of mTOR could potentially be biomarkers for curcumin chemoprevention studies.

Objective: Extracellular matrix metalloprotease inducer (EMMPRIN) is highly over-expressed in head and neck cancer (HNSCC) and is thought to be induced by surrounding fibroblasts to stimulate matrix metalloproteases which modulate tumor cell invasion, growth and angiogenesis. We hypothesize that loss of EMMPRIN will inhibit the growth of HNSCC tumor cell lines in vivo. Methods: The HNSCC cell line, FaDu was transfected with EMMPRIN (FaDu/E), FaDu transfected with control vector (FaDu), or FaDu transfected with plasmid expressing small interfering RNA against EMMPRIN to assess the loss of this protein in the FaDu cell line. Results: EMMPRIN Knockdown in FaDu cells significantly decreased cell proliferation, cell invasion and matrix metalloprotease activity compared to control. Conclusions: EMMPRIN expression is a potential therapeutic target in HNSCC.
ed onto the flank of SCID mice (n= 5 per group). Tumors were measured biweekly for 30 days and then tumor samples analyzed for proliferation (Ki67 immunohistochemistry), microvessel density (Factor VIII), and apoptosis [TUNEL assay]. **Results:** Tumor growth positively correlated with increasing EMMPRIN expression; FaDu cells overexpressing EMMPRIN demonstrated tumor growth was significantly larger at four weeks compared to control vector transfected cells (p = 0.0061). Similarly, the control vector transfected FaDu tumors were significantly larger than knockdown EMMPRIN FaDu tumor cell derived tumors (p = 0.0004). Animal survival negatively correlated with EMMPRIN expression. Immunohistochemical analysis demonstrated increased Ki67 in EMMPRIN transfected cells, without a significant change in the rate of apoptosis between groups. Vascular density and tumor formation rate also increased significantly with EMMPRIN expression. These data suggest that MT1-MMP function as a direct-acting, pro-invasive factor that confers tumor cells with the ability to penetrate connective tissue barriers and initiate the metastatic cascade. The loss of EMMPRIN expression decreased cell proliferation and microvessel density of tumor cells.

**Conclusion:** EMMPRIN promotes tumor growth in a murine flank model suggesting that anti-EMMPRIN targeted therapy may prove to be an effective treatment option in head and neck squamous cell carcinoma. The loss of EMMPRIN expression decreased cell proliferation and microvessel density of tumor cells.

**S323: MT1-MMP MEDIATES TUMOR CELL TRAFFIC THROUGH THE EXTRACELLULAR MATRIX IN VIVO AS WELL AS IN VITRO**

**Objective:** The metastatic spread of tumor cells to distant organs via hematogenous routes represents the most important cause of morbidity and mortality in cancer. In order for malignant cells to extravasate into the host vascular compartment, tumor cells need to exhibit a decrease in invasion and motility profile, which allows them to infiltrate an ECM largely composed of a dense, cross-linked meshwork of type I collagen fibrils. To date, matrix metalloproteinase (MMP) are thought to play a key role in allowing the primary tumor to traverse the intervening extracellular matrix (ECM) barriers and extravasate through the vessel wall as a fibroblast-like phenotype. In this study, we investigated which MMPs can drive tumor cell invasion and metastasis in vitro and in vivo. **Methods:** Using fibroblasts isolated from gene-targeted mice, human head and neck squamous cell carcinoma (HNSCC) cells and human fibrosarcoma cells, collagen invasion assay and collagen degradation assay were performed to ascertain which MMP conferred proteolytic activity in vitro. Additionally, chick chorioallantoic membrane (CAM) assay was done as an in vivo invasion and metastasis assay. And also the siRNA technology was employed to knock down a targeted gene, such as a MT1-MMP, specifically. **Results:** Fibroblasts and tumor cells were able to tunnel through dense barriers of cross-linked type I collagen in vivo via a virtually indistinguishable proteolytic process that requires MMP activity. Further, we demonstrated that fibroblasts deficient for the membrane-anchored metalloproteinase MT1-MMP were unable to display pericellular collagenolytic activity and were incapable of expressing a collagen-invasive phenotype in vivo, using CAM assay. Likewise, gene silencing of MT1-MMP in human HNSCC or fibrosarcoma cells similarly resulted in a complete loss of membrane-associated collagenolytic activity and renders tumor cells unable to infiltrate host tissues. **Conclusion:** These data suggest that MT1-MMP functions as a direct-acting, pro-invasive factor that confers tumor cells with the ability to penetrate connective tissue barriers and initiate the metastatic process in vivo. Furthermore, we also showed the effect of MT2-MMP on cancer invasion.

**S324: SYNERGISTIC SUPPRESSION OF HEAD AND NECK CANCER GROWTH BY RETINOIC ACID AND DNA DEMETHYLATING AGENT, 5-AZACYTIDINE**

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**Objectives:** Despite combined surgery and/or chemoradiation therapies, the overall survival rate for HNSCC patients is among the lowest of major malignant tumors (50% overall 5-year survival rate). Over the years, a number of novel therapeutic regimens have been utilized in HNSCC with little success; the primary goal is to improve antitumor efficacy. The use of 13-cis-retinoic acid (RA) showed initial promise by successfully reversing oral premalignant lesions. However, several large clinical trials later showed that 13-cis-RA was not effective in preventing tumor recurrence and second primary tumors, or in improving patient survival in either head and neck or lung cancers. It was postulated that the low levels of retinoic acid leading cancer cells to succumb to the drug in part due to the decreased expression of various RA receptors [RARs]. In fact, it was shown that the expressions of RARα, RARβ, and RARγ were frequently decreased in HNSCCs, and that one of these genes, RARβ, was silenced through promoter methylation. Based on these observations, we hypothesize that the dismal results from 13-cis-RA treatment of HNSCCs are caused by combined epigenetic silencing of the RARs and high toxicity of 13-cis-RA that prohibits the use of higher doses of this agent and that treatment of head and neck cancer cells with a DNA demethylating agent, 5-azacytidine (5-AC), will re-activate some of these RAR genes and thus augment the antitumor effects of 13-cis-RA. In this study, we tested this hypothesis by investigating the in vitro tumor suppression and gene expression profile of RA signal transduction pathway in head and neck cancer cells treated with 13-cis-RA and 5-AC. **Methods:** Cultured head and neck cancer cells were treated without or with 5-AC and/or 13-cis-RA and cell proliferation was determined using CellTiter 96 Aqueous One Solution Cell Proliferation Assay. **Results:** 13-cis-RA and 5-AC showed robust, synergistic in vitro tumor suppression (70% suppression with 2 mM 5-AC and 10 mM 13-cis-RA) when compared with treatment with 2 mM 5-AC (28% suppression) or 10 mM 13-cis-RA (30% suppression) alone. By a two-factor analysis of variance (ANOVA) test, 5-AC demonstrated significant interaction effects with 13-cis-RA (p < 0.001), supporting a synergy between these two agents. Among 33,000 human genes in HNSCC microarray, there are 10 well-characterized RA responsive genes: retinoic acid receptors α, b, and g (RAR α, b and g); retinoic receptor responders 1, 2, and 3 (RARRES-1, -2, -3); cellular RA binding proteins 1 and 2; and retinoid X receptors a and b (RXRA and RXRB). Cells treated with 5-AC and 13-cis-RA (Polyn 1) and RARES-3 were markedly and synergistically induced (Figure 2). Bisulfite DNA sequencing revealed that RARES-3 gene was re-activated through reversal of its hypermethylated state in the promoter region (Figure 3). **Conclusions:** 13-cis-RA and 5-AC can robustly and synergistically suppress in vitro head and neck cancer growth and this synergistic tumor suppression is in part due to selective activation of two RA-responsive genes, RARES-1 and RARES-3 via reversal of promoter hypermethylation.

**OUTCOMES: GENERAL**

**S325: DEVELOPING QUALITY AND PERFORMANCE GUIDELINES FOR HEAD AND NECK SURGERY**


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**Purpose:** Health care expenditures continue to increase at a rate that outpaces inflation. The Institute of Medicine has raised concerns that patients are not consistently receiving optimum cancer care and advocacy for establishing quality standards are growing. In the future meeting quality standards may impact reimbursement and patient access. This study was undertaken to identify quality and performance standards that might apply to a tertiary head and neck surgical practice. **Methods:** Over 24 months 10 surgeons operated on 1014 patients. Procedures were divided into low acuity (LA) and high acuity (HA). There were 853 LA procedures typified by thyroidectomy, parotidectomy, and neck dissection. HA procedures (161) were laryngectomy, mandibulotomy, or major glossectomy with reconstruction. Each surgeon had a numeric code and parameters of stay (LOS), return to the operating room (OR) within 7 days, readmission within 30 days of discharge, wound infections, blood transfusions (BT) (12 month data only) and 30-day mortality. **Results:** For LA cases the mean LOS was 2.99 days (range 1.49 days). Surgeon specific differences between the lowest mean LOS and the highest was 4.46 days (p=0.005). Overall 1.4% of LA cases required a BT and the incidence by surgeon ranged from 0.3-4.9%. Eighteen (2.1%) patients were returned to the OR which ranged from 0-3.2%. Differences between surgeons were not statistically significant (p = 0.40). In the LA cohort the mortality and wound infection rates were 0.2% and not significant among surgeons (p = 0.15). For the HA cases the mean LOS was 10.73 days and ranged from 1-63 days. The differences between the mean LOS among the highest and lowest surgeon was a mean 3.49 days (p=0.05). Overall 21.7% of HA cases required a BT and ranged from 0-40%. P=0.20. Seventeen (10.6%) patients were returned to the operating room and ranged from 0-24%. In the HA cohort the mortality and wound infection rates were 3.1% and 10.6% respectively. Statistical differences in
rates of mortality and infection were \( p=0.76 \) and \( p=0.004 \) respectively. Of the 161 patients in the HA group admitted for their procedure, 26 or 16.1\% were readmitted. The highest and lowest readmission rates were 8.3-25\% (\( p=0.76 \)). **Conclusion:** Among the surgeons significant differences existed in the HA and LA cases for LOS and infection rates. No significant differences were found for blood utilization, 30-day mortality, readmission and return to the operating room. These data will serve as benchmarks for assessing variations in patient outcomes that are surgeon specific and identifying opportunities to implement best practices or other quality improvement measures.

**S326: DISPARITY BETWEEN CLINICAL AND PATHOLOGIC STAGING: RESULTS FROM A MULTI-INSTITUTIONAL ECOG/RTOG TRIAL**

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**Objective:** Treatment selection, clinical trial enrollment, and patient counseling are typically based on tumor staging, usually according to the American Joint Committee on Cancer (AJCC) criteria. Clinical staging is based on physical examination and radiographic findings which are readily obtainable for all patients. Pathologic staging requires surgical resection. More detailed information about tumor spread is derived through pathologic staging. This study compares the results of clinical and pathologic staging for a large cohort of head and neck cancer (HNSCC) patients treated with surgical resection in the course of a cooperative group study. The objective is to examine sources of disparity between clinical and pathologic stage. **Methods:** 560 patients with HNSCC were enrolled in a multi-institutional cooperative group study (ECOG 4393/RTOG 9614) over seven years. Entry criteria included cancer amenable to surgical resection with curative intent. Clinical staging was provided to ECOG/RTOG by the participating institution at enrollment. Stage at initial tumor diagnosis was used for recurrent cases. Surgical pathology reports were submitted after resection and pathologic staging was derived from them. Clinical outcome was collected semi-annually and submitted to the ECOG data center. Association of survival with stage was derived using the proportional hazards model. **Results:** 522 subjects completed surgical resection with complete gross tumor extirpation. Clinical or pathologic staging could not be obtained for 51 cases. Of the 471 cases with both surgical and pathologic staging, a disparity was found between the two methods in 192 instances (41\%). In 122 cases, pathologic stage was lower than the clinical stage, most often by one level. In 70 cases pathologic stage exceeded clinical stage. Primary site stage differed in surface extent (as estimated before resection and at the time of measurement by the surgical pathologist), or because of inaccurate clinical assessment of bony involvement. Nodal stage disparities arose when some or all clinically suspicious nodes were found to be free of disease (9\% of cases) or when nodal metastases were not detected preoperatively (21\% of cases including 53 N0 upgraded to N+ and 31 N1 upgraded to N2). Survival was significantly associated with pathologic T stage \( p=0.05 \) but not with clinical TNM stage \( p=0.20 \). **Conclusion:** There were disparities between clinical and pathologic stage in nearly half of all cases in this large multi-institutional study. Limitations in assessing the extent of primary tumor, distinct tumor borders on CT and MRI imaging studies, and limitations in nodal evaluation through palpation and imaging accounted for the differences. This demonstrates substantial limitations in clinical staging of SCCHN and may account for difficulties in correlating clinical staging with results for patients whose cancers are treated without resection.

**S327: NECK DISABILITY FOLLOWING RECONSTRUCTION WITH THE PECTORALIS MAJOR PEDICLED FLAP**

**P.V.Mouskarbel1, K.Fung1, J.Franklin1, R.Rastogi1, C.Anderson1, I.Yoo1, University of Western Ontario, London, ON, Canada**

**Objective:** The Pectoralis Major Pedicled Flap (PMPF) is widely used for head and neck reconstruction. Bulkiness and the associated gravitational down-pull are recognized disadvantages of this flap. Scarring, both at the recipient and donor sites, is expected. These factors may lead to neck range of motion (ROM) limitations, in particular flexion and extension. Our objective was to investigate the neck ROM and disability following PMPF compared to a control population. **Methods:** This was a retrospective cohort study that compared patients who underwent a PMPF procedure with a control group consisting of laryngectomized patients who were not reconstructed using a PMPF. Primary outcome measures were flexion and extension angulation excursion, clinical ROM and neck pain. Lateral cervical spine radiographs in the neutral, flexion and extension positions were obtained for all subjects. These were analyzed by a blinded radiologist. Angulations between the C2 and C6 vertebral bodies were measured for flexion, extension and neutral positions. The flexion and extension angulation angles from the neutral position were then calculated. A blinded physiotherapist measured the neck ROM for both groups. Finally, neck pain was measured using the Neck Disability Index (NDI) patient questionnaire. All results were then compared. A total of 23 patients with 23 PMPF cases and 23 control cases were enrolled. There were 9 patients in the study group and 8 in the control group. All patients, with the exception of one in the PMPF group, had undergone a laryngectomy procedure. All patients had received radiotherapy. The mean age for the study patients and the controls was 64.4 years and 59.5 years respectively. The mean time since surgery was 24.9 months in the study group (PMPF) and 37.1 months in the controls. The mean neck extension excursion angle was significantly reduced in the study group (4.5 degrees) as compared to the controls (13.4 degrees) \( p=0.039 \). The mean flexion excursion angle was similar in the study and control groups (28.5 vs. 28.4 degrees respectively; \( p=0.979 \)). Similar limitations were observed with the physiotherapist’s measurements. A significant difference was noted in neck extension (\( p=0.011 \)) but not flexion (\( p=0.212 \)). Neck pain as measured by NDI scores showed no difference between the two groups (\( p=0.913 \)). **Conclusion:** The pectoralis major pedicled flap is associated with significant limitations in neck range of motion when used for head and neck reconstruction. No neck pain-associated QOL impact was detected. A prospective cohort study is needed for further investigation and confirmation.

**S328: FUNCTIONAL REHABILITATION OF FIBULAR GRAFTED-SEGMENTAL MANDIBULAR DEFECTS VIA SOFT TISSUE MATRIX EXPANSION**

**O.K.Lim1, T.R.Bar1, N.Blanco2, G.K.B.Sandor1, 1University of Toronto, Toronto, ON, Canada; 2Sunnybrook Health Sciences Centre, Toronto, ON, Canada**

**Objective:** Vascularized fibular grafts are considered by many to be the gold standard for mandibular reconstruction. Fibula grafts have several advantages including long pedicle length, long length of available cortical bone and the possibility of including fascia, muscle and cutaneous tissue. However, when used to reconstruct segmental defects in a partially denuded mandible, the reconstructed bone volume may be inadequate for functional dental rehabilitation. The ‘double-barrel’ fibula graft has been used to address this problem, with encouraging results but is often limited by the span of the defect and increased technical demands. Surgeons have also attempted to alleviate this problem by performing supplemental corticocancellous iliac bone grafts via transoral approaches or vertical distraction osteogenesis of the fibula. These methods have proved successful but there is a considerable delay in functional rehabilitation with dental implants. This case series reviews the first reported use of soft tissue matrix expansion, or ‘tentpole’ reconstruction of fibular grafted-segmental mandibular defects in order to address the above limitations. **Methods:** A series of four patients with previous fibular grafted-segmental mandibular defects were treated using a soft tissue matrix expansion reconstruction technique utilizing iliac crest bone grafts and endosseous dental implants in order to provide functional dental rehabilitation. The patients were 2 males and 2 females with a mean age of 15.2 years. All patients previously underwent segmental resection of the mandible for various benign and malignant lesions and were primarily reconstructed with fibular grafts that resulted in inadequate bone volume for dental implant placement. None of the patients received radiation therapy to the mandible. **Results:** All patients had successful implant surgery with primary stability and no complications, with a follow-up ranging from 6 months to 5 years and a mean follow-up of 3.4 years. A total of 16 implants were placed into the reconstruction sites and all were osseointegrated (100\%) at the time of follow-up. Bony height was maintained at a level commensurate with the implants placed and was markedly greater than the pre-reconstruction fibula volume. Three of the four patients have been restored with the final dental prosthesis that remained in function at the time of follow-up and all report positive feedback with respect to function and esthetics. **Conclusion:** The reconstruction of mandibular segmental defects has become commonplace and is considered the standard of care by many. In order to overcome the deficient bone volume often found with fibula grafts, currently three options have been described in the literature: ‘double-barrel’ fibula, vertical distraction osteogenesis and supplemental corticocancellous iliac crest grafting via transoral approaches. All three options often provide adequate results; however the latter two require two additional surgeries to accommodate the ridge augmentation and then implant placement. The soft tissue matrix expansion, or...
Advances in reconstruction after head and neck cancer surgery have significantly improved the appearance of patients and their quality of life. Indeed, organ preservation therapies may preserve the anatomical structures but significantly change their physiology and function. Many variables confound direct comparison of different treatment methods. Beyond the TNM staging system, there is neither a widely accepted means to definitively grade oral functions that underlie patients' worst physical symptoms. In surgery to treat head and neck disease, we must consider the quality of life questionnaire version 4 (UWQoL) outcomes to detail of the anatomical resected, irradiated and reconstructed; secondly, to assess the Functional Rehabilitation Outcome Grades (FROG) as a method of accurately describing degrees of physical impairment objectively. Methods: A prospective cohort of 290 oral cancer patients treated with curative intent by primary surgery between 1999 and 2004, were studied. Those with advanced disease were treated with post-op (chemo-) radiotherapy. The resection specimen was weighed, and all muscles, nerves, bone mapped in theatre. Clinical and pathological staging noted. Eighty-one patients died of oral cancer or other causes during the period Aug 1999 to Dec 2007. After two to eight years of follow-up, 187 were disease free, of stable body mass and serially maintained steady Functional Intraoral Glasgow Scales (FIGS) measuring speech, chewing and swallowing. They were thus deemed to have reached a rehabilitation plateau, and then had their FROG assessment performed, and completed the UWQoL. Multivariate data analysis will be presented to identify predictors of oral functional embarrassment beyond TNM staging. Results: Having attained the rehabilitation plateau, two fifths of the survivors reported global UWQoL > 1000 points. This correlated with their global FIGS mean of 14.5 (max =15) patients, 17% had oropharyngeal resections, 47% had neck staging procedures, 95% were stage T2 or less, average resection weight was 9.4g, only 10% had irradiRx. In contrast, three fifths reported UWQoL< 1000. This correlated with a FIGS of 11.8, 34% had oropharyngeal resections, 79% had neck staging procedures, 31% had T3 or T4 tumors or had radiecentrosis, average resection weight was 23.2g, and 52% had radiotherapy. The weight (in grams) of the surgical specimen was a better predictor of functional loss than T stage alone. The anatomical structures surgically resected, sectioned or irradiated correlated with loss of objective function assessed by the FROG score. Conclusions: We advocate the routine weighing of the surgical specimen to assess the objective function in relation to the weight, and serially maintained steady Functional Intraoral Glasgow Scales (FIGS) measuring speech, chewing and swallowing. Thus, surgery with postoperative radiotherapy is likely to continue to play an important role in the management of this cancer, particularly in cases of advanced tumors with 01Cfunctionless01D larynges. The objective of the present study was to report the results of surgical treatment of SCC hypopharynx and to investigate factors predictive of loco-regional control and survival. Methods: Retrospective review of 106 (78 male) consecutive patients undergoing surgery with or without postoperative radiotherapy as primary treatment for SCC of the hypopharynx at Memorial/Sloan Kettering Cancer Center between 1986 and 2003. Mean age at diagnosis was 62.4 years. The tumor arose in the piriform sinuses in 90 patients, in the posterior pharyngeal wall in 14 patients, and in the post-cricoid area in 2 patients. Four patients had T1 tumors, 30 were T2, 48 were T3, and 24 were T4. 44% were clinically NO. Results: The median period of follow up was 29.6 months for all patients, and 61.4 months for surviving patients. The 5-year local control, regional control, disease-specific survival, and overall survival rates were 70.8%, 78.9%, 58%, and 37.5%, respectively. Postoperative radiotherapy significantly improved local control on univariate analysis (p<0.0001) but did not improve survival. Local control was also significantly affected by tumor subsite (p=0.003), surgical margins (p=0.03), previous head and neck cancer or radiotherapy (p<0.0001), comorbidity (p=0.001), and clinical N-stage (p=0.02). Tumor subsite, T-stage, and N-stage were also significant on multivariate analysis. Factors which had a significant impact on disease-specific survival included pre-operative vocal cord palsy (p=0.02), cartilage invasion (p=0.5), pathological T-stage (p=0.02), and pathological N-stage (p=0.004). The following factors significantly correlated overall survival: comorbidity (p=0.008), laryngeal invasion (p=0.04), pathological T-stage (p=0.02), pathological N-stage (p=0.02), extracapsular spread (p=0.0002), and presence of a fistula. Conclusion: Surgery with postoperative radiotherapy produces local control and survival rates which are comparable to those published using primary chemoradiotherapy. Tumor origin in the posterior pharyngeal wall, T-stage, N-stage, invasion of the larynx, and margin status are important prognostic indicators. Consideration should be given to more aggressive treatment in these patients.
This study confirms the high rate of postoperative complications in patients with advanced larynx and hypopharynx tumors. Postoperative complications occurred in 71.8% of patients. The most common complications were: nodal flu via (25.6%), partial flap necrosis (17.9%) and seroma (30.7%). The median follow-up period was 31 months. The study provides evidence that patients with psychosocial dysfunction following treatment for head and neck cancer benefit from a problem-focused psychosocial intervention. However, further research is warranted with a larger sample using a randomised controlled design within a multi-centred setting. Nevertheless, given the inherent limitation with any study such preliminary evidence is essential to inform future research.
new studies for head/neck cancer were reviewed and 6 successfully opened. 5 of these were treatment protocols and 1 was a tissue bank linked to a treatment protocol. In the first 7 months of combined effort 129 patients were screened for these clinical treatment trials. The RTOG cooperative group 1 affiliate membership goals were met in first 6 months of implementation. One investigator-initiated study was already open and the accrual goal for this was met 3 months after combining resources. A tissue study/tissue bank open prior to the combined effort saw a 38% increase in sample collection in the first 10 months. One investigator initiated trial is in the process of opening. Conclusions: The introduction of additional supportive services and combining resources from the CTO and the head & neck cancer program had a positive impact patient care and was successful in increasing participation in research.

S336: FACILITATION OF FOLLOW-UP IN HEAD AND NECK CANCER PATIENTS UNDERGOING TREATMENT A. Dhawan1, A.M. Shenoy1, K. Srividya 1, B. Premitha1, S. Duraisamy2, Kidwai Memorial Institute of Oncology, Bangalore, India; 2Kidwai Memorial Int Oncology, Bangalore, India

Objectives: Post treatment surveillance is a prominent part of oncologic practice to provide timely salvage intervention. However, the compliance of the patient to follow-up schedule remains dismal in spite of educating them about the virtues of regular follow up. The aims of this study is to assess the impact of certain simple measures in improving compliance to follow up such as giving follow up cards, acquiring four to five addresses of the patient for sending written communications to defaulter and providing travel concessions to the patient and to quantify whether the patient quality of life, post treatment, has any effect on the follow up patterns of the patients.

Methods: Sixty consecutive patients having head and neck cancer (larynx group 1 n=21; tongue group 2 n=19; parotid group 3 n=20), who underwent surgery from January 2004 to August 2004 at the institute, comprised the study material. The pattern of follow up was studied in three groups. Results: The patient groups 1 & 2 had a regular follow up for a period of two years (90% and 94%, respectively) and then defaulted (66.6% and 57%, respectively) and 3. Groups: Patients undergoing other functionally non-dEBilitating surgery (group 3) came for regular follow up for only one year (90%) and then defaulted. Conclusions: Follow up pattern after surgery is dependent on functional outcome of surgery and quality of life of the patient. Adherence to follow up can be positively enhanced by following certain simple measures like giving follow up cards, addresses to maintain written communications and giving travel support.

S337: PSYCHOMETRIC TESTING OF THE QOL-UW CHINESE VERSION IN TAIWAN Y. Lai1, C. Chan2, P. Chu2, S. Guo2, 1College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China; 2Department of Otolaryngology, Taipei VGH, Taipei, Taiwan, Republic of China; 3College of Nursing, U Toronto, Toronto, Canada

The purpose of this two-phase study were to (1) develop a Chinese version of the Quality of Life: University of Washington (QOL-UW) version 4.2 (2) examine the psychometric properties of, and (3) apply the QOL-UW to assess the quality of life in selected head and neck cancer patients in Taiwan. In phase I, instrument translation, content validity and feasibility were conducted. In phase II, the QOL-UW was tested in three major groups of head and neck cancer patients, including oral cavity cancer (N=120), laryngeal cancers (N=120), and hypopharyngeal cancer (N=70), with total 310 subjects. The results showed that (1) the QOL-UW version 4.2: Chinese has satisfactory face validity, content validity, feasibility, and internal consistency reliability; (2) construct validity was supported by the results of the significant correlations among QOL-UW and related factors; and (3) items in the QOL-UW are generally sensitive to detect the and reflect the few different char-acteristics of the above mentioned three types of head and neck cancers. Generally, patients have different levels of problems in swallowing, eating, communication, comfort and selected uncomfortable symptoms and these problems could be reflected by UW-QOL version 4. In conclusion, the UW-QOL version 4.2 is a brief and easily applied clinical and research tool to assess the quality of life of head and neck cancers patients.

S338: PROJECT OF SOCIAL RESPONSIBILITY FROM ONCOLOGY INSTITUTE OF PARANÁ: TOBACCO - A MATTER OF CON-SCIOUSNESS P.G. Pedruzzi1, J.C. Linhares2, G. Precoma2, C.N. Yamanouchi3, J.F.C. Camargo4, L.A.N. Dias5, R. Cravo6, 1Hospital Ernesto Gประกอบ; 2Hospital Curitiba; 3Hospital de Oncologia de Parana; 4Instituto de Oncologia de Parana; 5Companhia Celeste de Teatro; 6Hospital Curitiba

Objective: Curitiba is the capital of Paraná State located in the south of Brazil, and is the second capital in Brazil in number of smokers aged 15 and over. 80% of adult smokers started smoking before the age of 18 and worldwide tobacco use among adolescents is increasing mainly among girls, and also particularly in developing countries. According to the American Cancer Society, the earlier you start smoking, the more likely you are to develop long-term nicotine addiction. The aim of the project is to stimulate the discussion about tobacco harms in classroom and to create critical consciousness against tobacco. Method: At Institute of Oncology of Paraná (IOP) designed and performed the campaign of prevention of tobacco addiction in schools starting in 2007. It consists on an educational theater playing focus on tobacco prevention in the classrooms. It has been performed in public and private schools. The target public is children 10 years of age and older. On stage, a teenager who wants to start smoking talks with his conscience and shows the conflict of not being accepted by his group. The theater play warns against harmful substances found in tobacco, industry strategies to get new smokers, passive smoking and ways to help people stop smoking. Results: Up to now, the play was performed in fifty schools. The students have been quite motivated and interested in debating the subject. Conclusions: By reaching the young public, we can make primary prevention campaigns in an effective and inexpensive way.

S339: META-ANALYSIS OF SURGICAL TECHNIQUES FOR THE PREVENTION OF THE SEQUELAE OF PAROTIDECTOMY J.A. Corrêa1, N. King1, K. W.Fisher1, E.A. Pribitkin1, K. N. Heffelfinger1, D. Reiter1, 1Thomas Jefferson University, Philadelphia, PA

Objective: This study uses formal meta-analysis to evaluate the success of multiple methods for minimizing common complications of parotidectomy, specifically facial nerve paralysis, facial sialo-fistula, and facial numbness. Methods: Using a PubMed search through December of 2007, 70 articles were identified reporting results of management methods for one or more of the complications of parotidectomy described above. Cochrane’s RevMan (TM) software and methodology were used for formal meta-analysis of the 49 studies meeting inclusion criteria. Studies were scored on quality, the data were dichotomized (‘favoring intervention’ vs ‘favoring no intervention’), the statistical significance of the findings was calculated, and the findings reported in clinical context. Results: The mean Strength of Recommendation Taxonomy (SORT) score for all studies was 2.33. Meta-analysis of controlled studies of multiple techniques for prevention of facial contour deformity, clinical Frey’s syndrome, and positive starch test favored intervention with a cumulative odds ratio of 3.80 (95% CI: 2.89, 4.99); 6.59 (95% CI: 4.48, 9.69), and 5.80 (95% CI: 3.67, 9.17), respectively. Analysis of prospective controlled data favors preservation of the greater auricular nerve for reducing the incidence of auricular numbness, with an odds ratio of 7.48 (95% CI: 2.99, 18.73). Despite the high volume of reports proposing it, use of a modified rhedectomy incision could not be correlated with reduction in complications in this study because published data was inadequate for meta-analysis and not readily available. Conclusions: Meta-analysis confirms the utility of commonly published methods to reduce complications of parotidectomy. Interposition of any of a number of loco- regional flaps between the resection bed and the overlying skin is more likely than chance to reduce the incidence of post-parotidectomy Frey’s Syndrome. Interposition of SMAS, sternocleidomastoid muscle, or fat is more likely than chance to reduce the incidence of auricular asymmetry after parotidectomy. Attempted preservation of the greater auricular nerve is more likely than chance to reduce the incidence of auricular numbness after parotidectomy. There are insufficient published data to stratify these results for specific barrier materials, anatomic structures used, or technical variations. Although most of the described flaps, grafts and surgical techniques are significantly associated with meaningful improvement in outcomes, none is associated with dramatic (>80%) likelihood of success.

S340: AIRWAY ASSESSMENT PRIOR INSERTION OF FEEDING GASTROSTOMIES IN PATIENTS UNDERGOING TREATMENT FOR HEAD AND NECK CANCER R. Oakley1, J.Jeannon1, R.Salter1, M.O’Connell1, F.Calman1, T.Wong1, 1Leverhulme Trust, London, United Kingdom

Objectives: Feeding gastrostomies (FG) are well-established as a method of providing adequate nutritional support in patients undergoing treatment for head and neck cancer (HNC). These FG can be inserted percutaneously (PEG), under radiological guidance (RIG) or surgically (OG). The presence of a malignancy of the upper aero-digestive tract (UAT) introduces the potential risk of iatrogenic complications additional to those usually associated with PEG placement. These include abdominal wall metastasis (AWM) and airway obstruction (AO) due to tumour directly occluding the airway.
Objective: An examination of swallowing function after frontalateral vertical partial laryngectomy (FLVPL) is important for the preservation of laryngeal function. This method is suitable for early laryngeal cancer cases or post-irradiated recurrent cases. There are many reports of vocal function after FLVPL, but few studies on swallowing function. The purpose of this study was to reveal not only onco logical local control, survival rate) results but also the swallowing function of patients treated with FLVPL.

Method: Surgical treatment consisted of FLVPL and reconstruction with local skin flaps. This method had two steps. The first a laryngocutaneous fistula was made instead of tracheotomy, the second the fistula was closed by hinged flaps after few months. Twenty-eight patients underwent FLVPL from 1993 to 2006. Of the 29 patients, all patients were male, whose age ranged from 39 to 85 years (median 65). Clinically, there were 21 patients with T1, 5 patients with T2, 2 patients with T3, and one patient with T4. There were 17 post-irradiated recurrent cases. We recorded the number of days after surgery that patients resumed eating and examined their swallowing function by videofluorographic study.

Results: The overall disease control rate and laryngeal preservation rate were 87.1% and 79.3%, respectively. A significant postoperative surgical complication was noted in 6 patients (21%), and 5 of 6 were postirradiated recurrent cases. The predominant significant surgical complication was wound infection (3 patients; 10%). There was no patient with aspiration pneumonia. The incidence of completion laryngectomy due to functional problems was 0%. All patients could take meals in orally and resumed meals 2.8 days postoperatively on average. 22 cases (76%) could start a meal within 3 days after the procedure. There were six patients who had the videofluorographic test. Five out of six patients had very good swallowing function at the beginning of this study. The remaining case showed a slight disorder of swallowing function of the tongue base, larynx, and hypopharynx. These patients should be identified during initial assessment and should have a RIG or their PEG inserted under GA.

Conclusion: Airway complications during PEG insertion are rare but can be fatal. Identification of patients at risk of AO prior to PEG insertion is essential and requires a multidisciplinary team approach. Patients with the most risk factors are those with locally advanced tumor invading the tongue base, larynx, and hypopharynx. These patients should be identified during initial assessment and should have a RIG or their PEG inserted under GA.

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pH-dependent growth was determined by growth in 0.33% agarose. **Results:** Real-time RT-PCR analysis of 12 matched PTC-normal patient samples showed an average -28 fold increase (P = 0.005) in ALOX5 mRNA in tumor tissue and a linear trend correlating ALOX5 mRNA expression with Tumor Invasive Score (TIS) (P = 0.04) determined from clinical pathology reports. ALOX5 protein expression in the patient samples was validated by immunohistochemistry and data also indicated increased expression in cancer compared to normal tissue. To investigate this therapeutic potential of targeting ALOX5 expression in PTC, we tested the effect of Zileuton (0.01 uM to 50 uM) on the PTC cell lines, BCPAP, BCPAP transduced with ALOX5 (ALOX5-BCPAP) and BCPAP transduced with green fluorescent protein fused to ALOX5 (ALOX5-GFP-BCPAP). **XTT analysis after 48 hrs of treatment revealed no change in cell viability. Furthermore, the same cell lines treated with arachidonic acid (AA) or 5-hydroxyeicosatetraenoic acid (5-HETE) (0.01 uM to 1.00 uM) also showed no change in cell viability at 48 hrs. However, ALOX5-BCPAP showed a 3.54 fold increase (P = 0.0003) in percent invasion through 8 µm membrane pores overlaid with matrigel matrix compared to BCPAP transfected with vector alone. Fifty micromolar Zileuton treatment of ALOX5-BCPAP reduced invasion by 56% (P = 0.005). Additionally, ALOX5-BCPAP cultured in 0.33% agarose showed a 2.17 (P = 0.006) fold increase in anchorinpedependent growth. **Conclusions:** ALOX5 expression correlates with tumor invasion both in vivo and in vitro. Further, the invasive phenotype can be inhibited in vitro with the specific ALOX5 inhibitor, Zileuton. Significantly, inhibition of ALOX5 expression with Zileuton did not affect cell viability, in contrast with published reports that inhibition of ALOX5 in cancer cells, by pan-lipoxygenase inhibitors, results in death. Thus, our data indicate that ALOX5 expression in PTC correlates with tumor invasion and over-expressing ALOX5 in PTC cells increases the invasive phenotype, but does not affect cell viability. Thus, ALOX5 may be useful as a potential biomarker and therapeutic target for PTC.

**S344: ZD6474 CAUSES SIGNIFICANT INHIBITION OF ANAPLASTIC THYROID CANCER IN AN ORTHOTOPIC MURINE MODEL**

**M.K. Gulya1, D. Sano1, Z.L. Milas1, M. Zhao2, A.S. Jasser1, J.N. Myers1, 1MD Anderson Cancer Centre, Houston, 2MD Anderson Cancer Center, Houston.**

**Objective:** To examine the dual inhibition effect of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) using a small molecule tyrosine inhibitor, ZD6474 (Vedantam), on anaplastic thyroid cancer (ATC) both in vivo, using an orthotopic nude mouse model, and in vitro. **Methods:** In vitro we investigated the effects of ZD6474 on proliferation in multiple ATC cell lines using a proliferation (MTT) assay. The pro-apoptotic properties of ZD6474, when used in the ATC cell line ARO, were examined using flow cytometry and propidium iodide (PI) staining. In vivo, orthotopic xenografts in athymic nude mice were established using the ATC cell lines ARO and DRO, transfected with a luminescent luciferin gene. The mice were then randomized based on luminescent measurements of in vivo tumor growth and given 2 weeks of therapy prior to tumor volume measurement and histologic examination. **Results:** ZD6474 inhibited tumor cell proliferation in all 6 ATC cell lines (ARO, DRO, HTH 74, Kat-4, C643 and ATC-A) with IC50 values ranging from 2-10.4 µM. PI staining of ARO cells treated with ZD6474 exhibited 16.6% apoptosis at 8 µM. In vivo, ZD6474 treatment resulted in a 73.2% tumor volume reduction in the DRO cell line with mean tumor volumes of 138 mm3 (control) and 37 mm3 (ZD6474). Similarly, ARO cell lines had a 97% tumor volume reduction with mean tumor volumes measuring 40.3 mm3 (control) and 1.3 mm3 (ZD6474). **Conclusion:** Our data suggests that ZD6474 causes significant inhibition of ATC both in vitro and in vivo and may be a viable therapeutic agent for clinical use in ATC.

**S345: A NOVEL MECHANISM OF THYROID TUMORIGENESIS BASED ON INACTIVATION OF P53 BY THE PTG-BINDING FACTOR PBF**

**D. Kim1, M. Reid1, A. Turnell1, J. Watkinson1, J. Franklyn1, C. McCabe1, 1University of Birmingham, Birmingham, United Kingdom**

**Background:** The pituitary tumor transforming gene binding factor (PBF) is a poorly characterised gene that is over-expressed in pituitary and thyroid tumours. Recently, we showed that subcutaneous expression of PBF elicited tumours in nude mice, and expression correlates with thyroid tumour recurrence in man. Given the established role of ionising radiation in thyroid tumorigenesis, we have now investigated the relationship between PBF and the tumour suppressor gene p53, a central component of the DNA damage checkpoint. **Results:** Glutathione S-transferase pull-down assays showed direct binding of PBF to p53. Through mutational analysis, two regions of p53 were necessary for binding PBF between amino acids 160-318, and 319-393. Conversely, by disrupting PBF sequences, we observed that the N-terminal region of PBF is essential for p53 interaction, with binding abrogated by removal of two N-terminal regions between amino acids 28-93 and 93-149. We next showed that PBF can influence p53-mediated gene regulation through HeLa promoter assays in p53-null H1299 cells. PBF failed to modulate promoter activity in a non-malignant control malignant tumours where PBF is over-expressed, we propose a novel mechanism for response through modulation of p53 activity. Furthermore, in thyroid tumours where PBF is over-expressed, we propose a novel mechanism for endocrine tumorigenesis, whereby PBF binds specifically to P53 and inhibits its regulation of critical downstream genes involved in maintaining cellular and genetic stability.

**S346: WITHDRAWN**

**S347: PRESENCE OF GENETIC AND EPIGENETIC ALTERATIONS IN PAPILLARY THYROID CARCINOMA AND HASHIMOTO THYROIDITIS**

**M.S. Kokaota1, L.L.2, S. Schichman1, B. R. Smoller2, J.Y. Suen2, C. Tan1, Central Arkansas Veterans Healthcare System and UAMS, Little Rock, AR, 2University of Arkansas for Medical Sciences, Little Rock, AR**

**Objective:** Chronic inflammatory conditions are known to contribute to the development of malignancy. Hashimoto’s thyroiditis (HT) is an autoimmune-mediated chronic inflammatory condition in the thyroid gland which is often seen with papillary thyroid carcinoma (PTC) on histopathology. The activation of ret-PTC-1, frequently seen in PTC has been detected in HT, raising the possibility that long-standing HT may predispose thyroid epithelia to malignant transformation. Aberrant genetic (gene coding sequence mutations or deletions) and epigenetic (gene promoter methylation) alterations frequently occur and in some instances interact with each other in silencing critical tumour associated genes during the development of a wide variety of human cancer including malignant thyroid epithelial cancer. To further explore the relationship between HT and PTC, we perform analysis of loss of heterozygosity (LOH) analysis for gene deletion of hOGG1, a major repair gene for oxidative DNA damages, and promoter methylation of thyrotropin receptor (TSHR) gene in HT. **Results:** hOGG1 LOH was observed in 3 of 6 (50%) HT, but not in normal thyroid (0 of 16, 0%). Additionally, ALOX5-BCPAP cultured in 0.33% agarose showed a 2.17 (P = 0.006) fold increase in anchorindependent growth. **Conclusions:** ALOX5 expression correlates with tumor invasion both in vivo and in vitro. Further, the invasive phenotype can be inhibited in vitro with the specific ALOX5 inhibitor, Zileuton. Significantly, inhibition of ALOX5 expression with Zileuton did not affect cell viability, in contrast with published reports that inhibition of ALOX5 in cancer cells, by pan-lipoxygenase inhibitors, results in death. Thus, our data indicate that ALOX5 expression in PTC correlates with tumor invasion and over-expressing ALOX5 in PTC cells increases the invasive phenotype, but does not affect cell viability. Thus, ALOX5 may be useful as a potential biomarker and therapeutic target for PTC.

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**Background:** The pituitary tumor transforming gene binding factor (PBF) is a poorly characterised gene that is over-expressed in pituitary and thyroid tumours. Recently, we showed that subcutaneous expression of PBF elicited tumours in nude mice, and expression correlates with thyroid tumour recurrence in man. Given the established role of ionising radiation in thyroid tumorigenesis, we have now investigated the relationship between PBF and the tumour suppressor gene p53, a central component of the DNA damage checkpoint. **Results:** Glutathione S-transferase pull-down assays showed direct binding of PBF to p53. Through mutational analysis, two regions of p53 were necessary for binding PBF between amino acids 160-318, and 319-393. Conversely, by disrupting PBF sequences, we observed that the N-terminal region of PBF is essential for p53 interaction, with binding abrogated by removal of two N-terminal regions between amino acids 28-93 and 93-149. We next showed that PBF can influence p53-mediated gene regulation through HeLa promoter assays in p53-null H1299 cells. PBF failed to modulate promoter activity in a non-malignant control malignant tumours where PBF is over-expressed, we propose a novel mechanism for response through modulation of p53 activity. Furthermore, in thyroid tumours where PBF is over-expressed, we propose a novel mechanism for endocrine tumorigenesis, whereby PBF binds specifically to P53 and inhibits its regulation of critical downstream genes involved in maintaining cellular and genetic stability.
a significant challenge. Various immunohistochemical markers for thyroid malignancy have been proposed but no one marker has proven its ability to identify specific thyroid malignancy from benign disease. **Hypothesis:** Recursive Tree-based Partitioning Analysis can predict a unique molecular signature for distinguishing malignant thyroid carcinomas from benign disease. **Methods:** Using tissue-microarray techniques, a panel of 37 benign and malignant thyroid tumors was evaluated using immunohistochemistry for expression of 5 live and one patient be overexpressed in thyroid malignancy. The proteins examined were Galectin-3, HBME1, Cyclin D1, MMP11 and beta-catenin. Protein expression was evaluated separately for intensity, percentage, and subcellular localization by three investigators. Subsequently, recursive tree-based partitioning analysis with computer-mediated pruning (RTTree) was used to generate predictive algorithms. These algorithms were then subjected to test-set / training-set verification using a separate cohort comprising thyroidec-omies performed in a single year from a different institution. **Results:** A total of 68 thyroid specimens were evaluated. In the training set (n=37) there were 11 papillary carcinomas, 5 follicular carcinomas, 5 medullary carcinomas, 2 anaplastic carcinomas, 10 benign nodular disease and 4 normal thyroid specimens. In the test set (n=32) there were 18 papillary carcinomas, 3 medullary carcinoma and 18 benign nodular disease specimens. Recursive tree-based partitioning analysis with pruning at p=0.01 successfully generated predictive algo-rithms for distinguishing malignant from benign disease (p=0.001), follicular carcinoma from all other specimens (p=0.0001), and papillary carcinoma from all other specimens (p=0.0001). These algorithms associated with 74%, 97% and 100% of cases. The signif-icant predictive variable in final pruned algorithms were Galectin-3 per-cent age of cells positive, presence of HBME apical membrane coalescence, HBME1 intensity and HBME1 percentage of cells positive. Independent test set verification of these algorithms demonstrated robust predictive value for distinguishing malignant from benign disease (p=0.0001) with a sensitivity of 100%, specificity of 94%, and accuracy of 97%. The algorithm for pre-dicting papillary carcinoma from all other specimens generated predictive value. The signif-icant predictive variable in final pruned algorithms were Galectin-3 percent age of cells positive, presence of HBME apical membrane coalescence, HBME1 intensity and HBME1 percentage of cells positive. Independent test set verification of these algorithms demonstrated robust predictive value for distinguishing malignant from benign disease (p=0.0001) with a sensitivity of 100%, specificity of 94%, and accuracy of 97%. The algorithm for predicting papillary carcinoma from all other specimens (p=0.0001) demonstrated a sensitivity of 50%, specificity of 100%, and accuracy of 78%. **Conclusions:** The combination of Galectin-3 and HBME1 immunohistochemistry using the specific guidelines generated may be of predictive value in determining malignant from benign thyroid disease. Of note, this is the first study demonstrating possible clin-ical significance for apical membrane coalescence of HBME1 in thyroid carcinoma. Further investigation, especially into the utility of these findings in predicting follicular carcinoma from benign nodular disease is warranted.

S349: THE INFLUENCE OF PREVIOUS RADIATION ON PATHO-LOGICAL FEATURES AND CLINICAL OUTCOME IN PATIENTS WITH THYROID CANCER

P.M. Seaberg 1, S.Eski 2, J.L. Freeman 3, 1University of Toronto, Toronto, ON, Canada; 2Mount Sinai Hospital, Toronto, ON, Canada

**Objectives:** To determine whether prior head and neck radiation was related to less favourable pathology and clinical outcome in a cohort of patients presenting for surgical management of thyroid cancer. **Methods:** A retrospective chart review of patients included in the thyroid cancer data-base (1963-2005) at our institution. All patients diagnosed with thyroid cancer who had been treated for prior head and neck irradiation exposure prior to surgery were included. Relevant patient, radiation exposure, pathology, treatment, and outcome data were collected. **Results:** One hundred and five patients (83 female, 22 male) were included. The nature of radiation exposure was reg-istered. Diagnosed included 94 (86.6%) papillary carcinomas, 5 (4.7%) fol-licular adenocarcinomas, 4 (3.8%) Hurthle cell tumours, 1 (0.9%) medullary carcinoma, and one patient (0.9%) with toxic nodular goiter. Twenty-four patients had metastases to cervical lymph nodes. Twenty-three patients had extrathyroidal extension of disease. 22 had lymphovascular invasion. Nine (8.5%) patients had evidence of residual/recurrent disease; an additional 1 (10.4%) patients had metastases to at least one of bone, lung, liver, or brain. Five patients (4.7%) had a history of thyroid cancer. **Conclusions:** In total, 38% of the thyroid nodules containing CC were informed as benign by FNA. 23% corresponded to papillary thyro-carinoma. CC increased significantly with the malignant thyroid tumors with CC 

S350: INCIDENTAL PAPILLARY THYROID MICROCARCINOMA - A HARMLESS CONDITION?

A.Madrid 1, L.Castro 2, J.Niedmann 1, M.Dominguez 1, R.Rossi F 2, H.Amaral 1, L.Castro 1, Clinica Alemana, Santiago, Chile

**Introduction:** Incidental Papillary Thyroid Microcarcinoma (IPTM) is defined as Papillary Thyroid Carcinoma (PTC) equal or less than 10 mm in diameter. Due to improvements in thyroid ultrasonography (US), IPTM is now-adays increasingly being found. US allows detection and diagnosis of PTC by means of fine needle aspiration (FNA) and cytology, even tumors of 3-4 mm in diameter. Nodules smaller than 10 mm in diameter should be studied with FNA if they have suspicious US findings. **Objectives:** To determine the frequency of incidental IPTM in our series and analyse its association with cervical metastases. **Methods:** We reviewed data from our consecu-tive series of patients submitted to FNA and studied histology (blood clot technique) in a 4 year period (n = 1097 nodules). There were 153 (13.9%) positive FNA for Papillary Thyroid Carcinoma (PTC). Within this group, we selected those nodules equal or less than 10 mm and reviewed their definitive histology and US findings. **Results:** IPTM was found in 73 of 153 (49%) PTC nodules, measuring between 4 and 10 mm. The 73 IPTM were detected in 66 patients (59 women, mean age 44.3). Seven patients (9.5%) presented lymphatic metastases detected by US (7 in central compartment and 5 also in mid-jugular nodes, group III). The loca-tion of the primary tumor was subcapsular in all metastatic IPTM cases and in 73 of the non-metastatic cases (p<0.12). All US findings suggesting lymph node involvement were confirmed by surgery. **Conclusions:** The increasing use of US has allowed early detection of PTC. In our series 94% carcinomas were detected with US. The use of US and the lymphatic metastases at the time of diagnosis. Our results strongly support the use of US for pre-surgical assessment of cervical lymph nodes. Subcapsular loca-tion was not associated with increased risk of nodal metastases.

S351: COARSE CALCIFICATIONS IN THYROID NODULES - DO THEY RULE OUT MALIGNANCY?

E.Horvath 1, S.Majlis 1, A.Madrid 1, L.Castro 2, E.Soto 1, H.Rojas 1, F.Capdeville 1, H.Tala 1, M.Dominguez 1, R.Rossi F 2, Clinica Alemana, Santiago, Chile; 2Clinica Alemana, Santiago, Cocos (Keeling) Islands

**Introduction:** The ultrasonographic finding of coarse calcifications (CC) is usually associated with benign lesions. Is this also valid in case of thyroid nodules? **Objectives:** To evaluate the prevalence of thyroid nodules with CC in our series and their role as predictor of benign or malignant disease. **Methods:** We reviewed data from our consecutive series of patients sub-mitted to fine needle aspiration (FNA) (19G) and studied histology (blood clot technique) in a period of 4 years (n=1097). We defined as CC all those calcifications greater than 2 mm, on an arbitrary basis. Before FNA, the ultrasonographic characteristics of every nodule were analyzed. The Chi square Test was used to evaluate association between coars cal-cifications vs/s non-benign lesions on FNA (follicular lesion and papillary car-cinoma). **Results:** We found 153 (13,9%) positive FNA for Papillary Thyroid Microcarcinoma. The proteins examined were Galectin-3, HBME1, Cyclin D1, E.Horvath 1, S.Eski 2, J.L.Freeman 2, 1University of Toronto, Toronto, ON, Canada; 2Mount Sinai Hospital, Toronto, ON, Canada

**Objectives:** To determine whether prior head and neck irradiation was related to less favourable pathology and clinical outcome in a cohort of patients presenting for surgical management of thyroid cancer. **Methods:** A retrospective chart review of patients included in the thyroid cancer data-base (1963-2005) at our institution. All patients diagnosed with thyroid cancer who had head and neck radiation exposure prior to surgery were included. Relevant patient, radiation exposure, pathology, treatment, and outcome data were collected. **Results:** One hundred and five patients (83 female, 22 male) were included. The nature of radiation exposure was reg-istered. Diagnosed included 94 (86.6%) papillary carcinomas, 5 (4.7%) fol-licular adenocarcinomas, 4 (3.8%) Hurthle cell tumours, 1 (0.9%) medullary carcinoma, and one patient (0.9%) with toxic nodular goiter. Twenty-four patients had metastases to cervical lymph nodes. Twenty-three patients had extrathyroidal extension of disease, and 12 had lymphovascular invasion. Nine (8.5%) patients had evidence of residual/recurrent disease; an additional 1 (10.4%) patients had metastases to at least one of bone, lung, liver, or brain. Five patients (4.7%) had a history of thyroid cancer. **Conclusions:** In total, 38% of the thyroid nodules containing CC were informed as benign by FNA. 23% corresponded to papillary carcinoma. CC increased significantly with the malignant thyroid tumors with CC 

**Clinical:** NPC/SinUS/Skull Base II

S352: salvage surgery for recurrent nasopharyngeal carcinoma using a partial maxillectomy approach

L.S. Na1, K.S. Lo2, 1Dept Otolaryngology, National University Hospital, Singapore, Singapore; 2Dept Otolaryngology, National University of Singapore, Singapore, Singapore

**Objective:** The local recurrence rate in nasopharyngeal carcinoma (NPC) is approximately 10%. Nasopharyngectomy is an alternative to a standard course of radiation for local recurrence. Approximately 50% of all local recurrences are rT1 to rT2 and amenable to nasopharyngectomy. Traditionally, open surgical access to the nasopharynx is associated with significant morbidity and often requires mobilization of both maxilla and palate. This limits the use for salvage for those with failure as well as maintenance of a reason-able quality of life in survivors. We have found that the nasopharynx and paranasopharynx as well as the pterygopalatine fossa can be
accessed without wide extensive mobilization of the maxilla or palate. Hence resection of rT1-rT2 tumors may be performed by a limited access via a partial maxillectomy approach. We report our early experience using a limited open surgical approach to minimize morbidity. Metho: Prospective cohort study of nine consecutive patients with rT1 (six patients) and rT2 (three patients) recurrent NPC were analyzed. All the patients underwent a partial maxillectomy, removing the medial wall as well as the anterior wall to the infra-orbital nerve. Prior to these operations, posterior nasal septum was also resected to allow visualization of the whole nasopharynx. No palatal mobilization was performed. The outcomes as well as complications were charted prospectively. Results: There were 9 patients (7 male, 2 female) with a mean age of 53 years. The median duration of follow up was 28 months (range 5 to 43 months). There was 1 patient with local recurrence at 43 months postnasopharyngectomy. All the other patients have no evidence of disease. The most common morbidity is post nasopharyngectomy headaches and there was a patient with atlanto-axial subluxation. There was no post operative hemorrhage. None of the patients required a tracheostomy and all the patients took oral diet on post-operative day one. There was no significant trismus interfering with mastication and oral consumption in any of the patients postoperatively. Speech was normal in all patients and none of the patients complained of the cosmetic outcome. The mean length of stay was 4 days. Conclusion: Early local recurrence of NPC can be treated surgically using a limited access via a partial maxillectomy approach. It has good local control, acceptable cosmetic outcomes, rapid post-operative recovery, and low complication rate with a short duration of hospitalization. It is an alternative approach for nasopharyngectomy in rT1-2 nasopharyngeal carcinoma.

S353: NASOPHARYNGECTOMY FOR RECURRENT NASOPHARYNGEAL CARCINOMA: A REVIEW OF PATIENTS AND PROGNOSTIC FACTORS S.Hao1, N.Tsang2, 1Chung Gung Memorial Hospital, Taipei, Taiwan, Republic of China; 2Chung Gung Memorial Hospital, Taipei, Taiwan, Republic of China

Objective: The purpose of this study is to report the local control and overall survival outcome of patients with nasopharyngeal carcinoma who received salvage nasopharyngectomy and to identify prognostic factors. Methods: Fifty-seven consecutive patients who had primary recurrence of NPC and underwent salvage surgery for curative intention from July 1993 to July 2007 were retrospectively reviewed. The follow-up time ranged from 5.1 to 150.3 months, median: 36 months. The recurrent NPC stage were stage I: 30, stage II: 10, stage III: 9 and stage IV: 8. Fifty patients had one course of radiation therapy while 3 had two courses of radiation therapy before salvage surgery. For the nasopharyngectomy, 4 underwent endoscopic approach, 35 underwent facial translocation while 18 had craniofacial resection. Postoperative adjuvant treatment included radiation therapy: 4, radiosurgery: 8, concurrent chemotherapy: 5. Results: The 5-year local control rate were T1: 59.3%F05, T2: 28.6%F05, T3: 53.3%F05, T4: 75.0%F05, and all stages: 54%F05. The 5-year overall survival rate were stage I: 67.2%F05, stage II: 38.1%F05, stage III: 30.0%F05, stage IV: 46.9%F05 and all stages: 52.6%F05. Univariate analysis revealed that parapharyngeal space involvement was a significant impact factor of local control. Multivariate analysis revealed that gender, margin status and adjuvant treatment type were significant impact factors of local control and secondary local recurrence and adjuvant treatment type were significant impact factors of survival. Conclusions: The results of this study reveal better outcome of salvage surgery than that of most published literature of reirradiation for recurrent NPC. Salvage surgery is a justified treatment for primary recurrence of NPC. Bad prognostic factors of local control include parapharyngeal space involvement on univariate analysis, margin status and adjuvant treatment type on multivariate analysis. Bad prognostic factors of survival include secondary local recurrence and adjuvant treatment type on multivariate analysis.

S354: ENDOSCOPIC TRANSPTERYGOID NASOPHARYNGECTOMY FOR THE TREATMENT OF NASOPHARYNGEAL CARCINOMA A.M.Zanation1, S.Alsheibani1, R.Carroll1, C.Snyderman1, A.Kassam1, 1University of Pittsburgh Medical Center, Pittsburgh, PA

Objective: To evaluate the outcomes of a selected population of patients with nasopharyngeal carcinoma treated with an endoscopic transpterygoid nasopharyngectomy. Methods: We performed a retrospective analysis of all patients who underwent endoscopic transpterygoid nasopharyngectomy for primary or recurrent nasopharyngeal carcinoma at our Cranial Base Center from January 2002 to June 2006. All surgeries were performed with curative intent. Our technique involves an endonasal endoscopic approach that includes an endoscopic anterior and inferior (Denkers) medi-al maxillectomy, removal of the posterior wall of the antrum, mobilization of the contents of the pterygopalatine fossa, removal of the pterygoid plates for access to the torus tubarius and fossa of Rosenmuller, and finally identification and control of the parapharyngeal and petrous internal carotid artery as the lateral margins. Intraoperative frozen sections help optimize complete tumor resection. Seven patients with stage Ill and stage IIV nasopharyngeal carcinoma underwent an endoscopic resection with curative intent. Five of the patients had persistent disease following radiotherapy and two patients were primary tumors treated with surgery then radiotherapy. In all cases, we were able to obtain negative microscopic margins. None of the endoscopic resections required a conversion to an open approach. We encountered no surgical mortality; however, one patient suffered an internal carotid artery injury which was successfully managed intraoperatively. The follow up ranged from 1 - 4.8 years with a mean of 2.07 years. At last follow-up, four patients (57%) showed no evidence of disease at the primary site. Conclusion: Endoscopic transpterygoid nasopharyngectomy is a feasible approach for treating primary and recurrent nasopharyngeal cancer.

S355: THE ROLE OF INDUCTION CHEMOTHERAPY IN THE MANAGEMENT OF SINONASAL UNDIFFERENTIATED CARCINOMA M.A.Dawson1, J.Goldgard1, D.Roberts1, S.Ibrahim1, N.Ark1, M.DeMonte1, E.Y.Hanna1, 1MD Anderson Cancer Center, Houston, TX

Objective: To investigate the utility of induction chemotherapy in the management of patients with sinonasal sinus malignancies. Introduction: Malignancies of the paranasal sinuses are generally treated with surgical resection and adjuvant therapy (typically, irradiation or chemoradiotherapy). However, sinonasal undifferentiated carcinomas (SNUC) are particularly aggressive tumors that respond poorly to conventional therapies. Based on recent studies that suggest a predictive value of response to induction chemotherapy in head and neck malignancies, we retrospectively evaluated the outcomes of patients treated with induction chemotherapy for SNUC at our institution. Methods: A retrospective review of 30 consecutive patients with SNUC treated with curative intent at our institution was performed. All patients underwent induction chemotherapy. The response to induction therapy was assessed by imaging evaluation 6 weeks after completion of therapy. The response was classified as either: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Their subsequent treatment was based on the response to the induction phase. The patients’ survival data was abstracted from their charts. Results: Of the thirty patients with SNUC evaluable for this report, there were 21 patients who had some response to induction (CR or PR) and 9 patients who were non-responders (SD or PD). Patients who responded to induction chemotherapy were 30-month disease free at a median follow-up of 86 months compared to non-responders. The 5-year survival was 70% vs 11% (p<0.05). Approximately 58% of responders (12/21) underwent consolidation therapy with chemoradiation without surgical resection. Discussion: Induction chemotherapy has a role in the management of patients with undifferentiated sinonasal malignancies. Patients treated with induction chemotherapy had improved overall survival. However, non-responders to induction chemotherapy had uniformly poor outcomes. Induction chemotherapy may allow us to stratify the appropriate patients to undergo surgical therapy, but further work is needed to refine the treatment strategy.

S356: STEREOTACTIC RADIOSURGERY FOR HEAD & NECK AND SKULL BASE CANCER A.Pinheiro1, N.Kim1, H.Kim1, 1St. John’s Clinic, Springfield, MO

Objective: Cyberknife (CK) is a form of stereotactic radiosurgery (SRS) which uses a linear accelerator with a robotic arm in order to deliver a highly focused radiation dose to extracranial tumor volumes. Cancer recurrence at the skull base usually portends poor prognosis and in patients who have undergone prior surgery and external beam radiotherapy (EBRT), treatment options are usually limited. We used CK SRS for treatment of recurrent and primary malignancies in patients who were not deemed candidates for further surgery and/or EBRT. Our aim is to review the safety, efficacy, and complications of CK in treating previously irradiated head and neck cancers. Methods: Non-randomized study with prospective data collection. Data from 9 tumor treatment sites (1 patient had same site treated on two occasions) were analyzed. All patients were presented at our multidisciplinary brain, spine and head and neck CK tumor conference. Treatment was planned for 3 consecutive fractions and delivered in our CK treatment facil-
ity. Results: Data from 8 patients were analyzed. Radiation dose ranged between 20-40 Gy and was delivered in 5 fractions. All but 1 patient had recurrent squamous cell carcinoma. One patient had the same tumor retreated with CK. The most common tumor location was sinus/skull base. All patients had received prior external beam radiotherapy to the treated area. Average tumor volume treated was 83 cubic cm. The most common complications were trismus and dysphagia requiring gastrostomy tube placement. In one case, recurrent aspiration pneumonia was encountered. Five patients died of disease (3 with distant metastases, one of which with no evidence of local disease), and at last follow-up 3 patients were alive with disease. Conclusions: SRS can be used to treat skull base and head and neck malignancy in previously irradiated fields. Local tumor control and palliation can be achieved with SRS even in this high risk population of heavily pre-treated patients. However, 37.5% of our patients developed distant metastasis which was a major cause of patients’ demise, suggesting that further systemic therapy may be an important determinant of survival. SRS is generally well tolerated, but patients do have risk of trismus and dysphagia which were manageable. In patients experiencing dysphagia, gastrostomy feeding is frequently required.

S357: MR-EVIDENT RETROPHARYNGEAL LYMPH NODE METASTASIS IN NPC PATIENTS: CLINICAL IMPACT S.Chin 1, C.Lin2, J.Chang2, 1Chang Gung Memorial Hospital at Linko, Tao-Yuan, Taiwan, Republic of China; 2Departments of Radiation Oncology, Tao-Yuan, Taiwan, Republic of China

Purpose: To investigate the retropharyngeal lymph node (RLN) metastasis in nasopharyngeal carcinoma (NPC) regarding the categories of incidence, overall survival, local control, and as a factor for defining false positives on PET/CT.

Method: A retrospective review of the medical record from 302 biopsy-proved NPC patients. All patients had undergone magnetic resonance imaging and had conventional radiotherapy as their primary treatment.

Results: MR is better than CT in recognizing the RLN from NPC with the incidence of RLN approximately 75.7%. By using univariate Kaplan-Meier analysis, it shows no significant difference of the overall and stratified T-stage survival, locoregional control and distal metastasis between patients with or without RLN metastasis. On the other hand, the presence of RP can effectively inhibit the tumor from spreading to the lateral neck lymphatic system and farther as evidenced by the better locoregional control in patients categorized as N3 or stage IV, and less distal metastasis in NO cases (p <0.05 respectively). Conclusions: RLN metastasis does not show a negative influence on the variety of prognostic factors in patients with NPC. Instead, in some circumstance, the presence of RLN is beneficial to bolster locoregional control and lessen the distal metastasis. MR is the imaging modality of choice in the detection of RLN.

S358: FALSE POSITIVES AND SPECIFICITY WITH PET/CT IN THE ASSESSMENT OF RECURRENT MALIGNANT DISEASE OF THE SKULL BASE G.Pitzer 1, R.J.Harvey 1, D.B.Nissman 1, Z.Rumboldt 1, R.J.Schlosser 1, 1Medical University of South Carolina, Charleston, SC

Objective: The identification of recurrent tumor in the skull base can be challenging. Altered anatomy, radiotherapy, hardware and reconstructive materials distort the field. Local granulation tissue and mucositis can lead to abnormal examination and misleading positron emission tomography/computed tomography (PET/CT) findings. The diagnostic characteristics of PET/CT in patients with suspected recurrent malignancy were assessed.

Methods: A retrospective review was undertaken of head and neck cancer patients who had PET/CT. 406 cases were included during an 18 month period. Histopathology and clinical course outcomes were correlated with PET/CT findings. The standard uptake values (SUVs) for the suspected recurrences site and the associated brain SUVs were recorded. Follow up clinical, endoscopic and radiological exams were used to update false positives and true negatives. Tumor type, location and biopsy results were recorded.

Results: Thirty four PET/CTs were performed for suspected recurrent malignancy in the skull base (mean age 59.6±15.7yrs, female 38%). The group comprised mainly of minor salivary (35.3%), squamous (32.3%) and neuroectodermal (20.6%) tumors. Mean clinical follow up after PET/CT was 256±173 days. Sensitivity was 100% but specificity was 40%. Thirty four PET/CTs represented a positive predictive value of 33.8%. SUVs for true positives were higher than false positives (p=0.018).

Conclusions: CT/PE is a highly sensitive test for malignant disease. However, positive findings have little meaning without an understanding of the clinical and endoscopic assessment of the area of interest. The mucosal lining of the reconstructed skull base is a common source for inflammatory pathologies that may lead to false positive CT/PE. Defining SUV thresholds for malig-nancy may improve specificity.

S359: GENE EXPRESSION AND PROMOTER POLYMORPHISMS OF DNMT3B IN NPCS IN TAIWAN: A CASE-CONTROL STUDY C.Chang 1, K.Fang 1, S.Hao 1, 1Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China

Objects: Over-expression of the gene DNMT3B and its effect on carcinogenesis has been shown for various types of cancers. Recently, three single nucleotide polymorphisms (SNPs) of the DNMT3B promoter region, C46359T (-149C > T), -238T > C, and -579G > T have also been reported to be stratification markers that can predict an individual’s susceptibility to cancers. However, the relative significance of the expression pattern of DNMT3B and these novel SNPs with regards to the genetic susceptibility of an individual to NPC in Taiwan, to the best of our knowledge, has not been determined. Therefore, the aim of this hospital-based case-control study was to examine the expression patterns of DNMT3B in NPC specimens and per- canorous normal counterparts, and determine whether these three novel SNPs of DNMT3B are actually risk factors for NPC within the Taiwanese population. Material and Methods: Subjects were recruited and enrolled into the study from consecutive patients presenting at an ongoing molecular epidemiological study being conducted within the Department of Otolaryngology – Head-and-Neck Surgery at Chang Gung Memorial Hospital, Tao-Yuan, Taiwan. All cases were newly diagnosed, previously untreated patients with NPC. All had had their condition histopathologically confirmed between September 1990 and November 2005, inclusively. No restrictions applied regarding participant age, gender, histological classification, and/or tumor stage. Control subjects were derived from a pool of volunteers attending the hospital as part of a routine health-examination program, including individuals presenting with otolaryngological-related, non-neoplastic diseases. The expression patterns of DNMT3B were determined by cDNA microarrays and RTPCR. The genotype of each of these three DNMT3B SNPs was determined using a matrix-assisted laser desorption / ionization time-of-flight / mass spectrometry (MALDI-TOF/MS)-based mini-sequencing method.

Results: In this study, we analyzed expression of DNMT3B in nasopharyngeal carcinoma (NPC) specimens and did not find elevated levels of DNMT3B in tumors using cDNA microarray analysis and RTPCR. Meanwhile, 259 NPC patients and 250 controls were genotyped for the above three SNPs using a MALDI-TOF based mini-sequencing method. For C46359T (-149C > T), only the T/T genotype was found to be present in both patient and control groups (100% frequency). The frequency of the genotypes, -238CT, -238TT and -238TT, amongst NPC patients versus controls was, respectively, 86.1% versus 84.0%, 13.5% versus 15.6%, and 0.4% versus 0.4% (P=0.589). The allele frequency, -238T and -597GG, for patients versus controls was, respectively, 87.3% versus 84.8%, 12.0% versus 15.2%, and 0.8% versus 0.0% (P=0.501).

The distribution of SNPs among cancer patients either featuring or not featuring central nervous system metastasis also did not differ significantly.

Conclusion: Our data indicate that neither over-expression of DNMT3B nor the presence of three DNMT3B SNPs are associated with NPC, which suggests that DNMT3B might not play a role in hypermethylation of many tumor suppressor genes during carcinogenesis of NPC.

S360: FASCIA-ONLY FREE RADIAL FOREARM FLAP FOR RESURFACING THE NASOPHARYNX FOLLOWING NASOPHARYNGECTOMY C.EH.Tee 1, M.L.C.Khoo 1, 1Tan Tock Seng Hospital, Singapore, Singapore

Objective/Background: We have previously described the use of the standard free radial forearm flap for resurfacing the nasopharynx following radical nasopharyngectomy. Despite its effectiveness in promoting healing and preventing carotid rupture, the skin lining of the flap has in some patients continued to cause crusting within the nasopharynx, necessitating regular nasal toilet. Therefore, since 2006, we have started using a fascia-only free radial flap to resurface the nasopharynx. We describe this modifi-cation and our results. Methods: Retrospective review of four patients who underwent radical nasopharyngectomy via a maxillary swing approach followed by resurfacing of the nasopharynx with a fascia-only free radial forearm flap. Results: After follow-up ranging from 6 to 18 months follow-up, all patients have had no signs of flap death or failure. The tissues have remained viable and healthy. The fascia of all the free radial forearm flaps has been covered by nasal mucosa and therefore does not create a barrier to the sinonasal cavity.

Conclusions: Resurfacing of the nasopharynx is important after radical nasopharyngectomy. The fascia-only free radial forearm flap appears...
to be even more effective than the traditional free radial forearm flap in achieving a good functional outcome.

**ORAL CANCER SCREENING/PREVENTION**

**S361: A POPULATION-BASED ANALYSIS OF THE ASSOCIATION OF ORAL/PHARYNGEAL CARCINOMAS WITH HPV-RELATED ANOGENITAL CANCERS IN MEN**

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**Objective:** Oncogenic human papillomavirus (HPV) has been linked to a subset of oropharyngeal and oral squamous cell carcinomas (SCCA), and is a well-recognized factor for other cancers including cervical, anal, and penile carcinomas. We used the Surveillance, Epidemiology, and End Results (SEER) cancer database to determine the strength of associations between oral and pharyngeal SCCA and anogenital carcinomas in men.

**Methods:** We used SEERSTAT software to identify patients from 1974-2004 with initial primary tumors of the oral cavity or pharynx (squamous histology only), anogenital region (squamous, basaloid, or cloacogenic), or selected HPV-unrelated primary sites (all histologies). Standardized incidence ratios for developing a second anogenital or oral/pharyngeal primary were calculated based on the observed number of cases divided by the expected number of cases based on the age- and sex-adjusted incidence of these cancers in the population.

**Results:** We identified 40,930 men whose first cancer was an oral or pharyngeal SCCA, for a total of 221,709 person-years of followup. Corresponding numbers for oral and penile cancers were 1,765 men (9,959 person-years) and 1,943 men (13,731 person-years) respectively. For men with first tumors in the oral cavity or pharynx, the relative risk of anal carcinoma was 2.12 (CI 1.19-3.30). The relative risk of developing oral/pharyngeal carcinoma for men with anal or penile cancer was 3.51 (CI 2.04-5.61) and 2.43 (CI 1.48-3.75) respectively. For second primary tumors of the tonsil, the relative risk was 8.4 (CI 2.73-19.59). A smaller increase in relative risk of oral/pharyngeal carcinoma was also observed for women with an index primary of the anus (2.32, CI 1.11-4.27). There was no increase in rates of oral/pharyngeal, or anogenital cancers in men with index cancers of the prostate, bladder, or colon (HPV-unrelated sites). The relative risks of anogenital and oral/pharyngeal second primary tumors in men did not vary significantly by age, race, or geographic location. However, risk of a second primary oral or pharyngeal cancer following anal cancer varied sharply by marital status: 1.83 (CI 0.60-4.28) for married/widowed men vs. 5.46 (CI 2.62-10.04) for unmarried men. An even more striking difference was seen for second primary tonsil cancer following anal cancer, where the relative risk for unmarried men was 17.72 (CI 4.83-45.37) and no cases were observed among married/widowed men. A similar trend was seen for the development of second primary anal carcinoma after oral/pharyngeal index tumors.

**Conclusions:** The markedly elevated risk of second primary anogenital tumors in men following oral and pharyngeal carcinomas, and vice versa, strongly supports a pathogenic role for oncogenic HPV in a subset of oral and pharyngeal SCCA. The dramatic increase in risk among men who had never been married, as compared to married or widowed men, suggests an interaction between sexual behavior and risk of HPV-associated cancers. Further analysis of population-based databases which include information about behavioral risk factors is required to determine the nature of this interaction.

**S362: LACK OF ASSOCIATION BETWEEN HPV INFECTION AND ORAL TONGUE CARCINOMA IN YOUNG AND OLDER ADULTS**


**Objectives:** Analyses of Surveillance and Epidemiology End Results (SEER) data have shown that from 1973 to 2001 there has been a significant increase in tongue and tonsil SCC incidence in younger adults aged 20-44 years (Shiboski et al. 2005). This increase contrasts with changes in SCC incidence rates for other oral cavity and pharyngeal sites in both this age group and in older patients, which have either decreased or stayed constant over time. Since there is a well established strong association between tonsillar SCC and HPV infection, we hypothesized that the increased incidence of oral tongue SCC among young adults may similarly be associated with HPV. The objective of this study was to compare the prevalence of HPV infection between oral tongue SCC in persons < 45 years of age and persons > 65 years of age.

**Methods:** HPV-DNA was extracted from 35 oral tongue SCC specimens from the UCSF Oral Cancer Tissue Bank, from persons < 45 years, and 35 specimens from persons > 65 years at time of diagnosis. DNA was extracted from formalin-fixed, paraffin embedded specimens and PCR performed using MY09/11 consensus primers followed by specific probing for 30 different HPV types. Specimens were also studied using GP5/6 primers and specific nested E6 PCRs for HPV types 16, 18, and 31. The band obtained from one specimen using type-specific PCR was sequenced.

**Results:** Among the 70 oral tongue SCC specimens analyzed for the presence of HPV, only one specimen was found to be positive for HPV. The HPV identified was type 16. The patient from whom this specimen was collected was a 72 year-old woman. The patient from whom this specimen was collected was a 72 year-old woman. The patient from whom this specimen was collected was a 72 year-old woman. The patient from whom this specimen was collected was a 72 year-old woman. No oral tongue SCC specimens among adults < 45 years were found to be positive for HPV, and only one specimen obtained among older adults was found to be positive. This study suggests a lack of association between oral tongue SCC and HPV.

**Objectives of the Study:** Squamous Cell Carcinoma of the Oral Tongue has increased in incidence 5 to 6 fold in the last 30 years in the Western World. However, the etiology of the disease, definition of young age, correct treatment strategy and outcome are still at question. Our goal is to examine the clinical and pathological features of SCCT in younger group of patients compared to an older group. Methods: The retrospective study cohort included 41 SCCT patients, divided into young (< 45y, N=18) and old (> 65y, N=23) groups. Minimal follow up at 2 years after diagnosis and sufficient treatment data were also necessary for inclusion. The 15-y gap between these groups was intended to confer a higher statistical validity to the influence of age on the results. The hematoxylin and eosin-stained slides of the resected specimens were assessed according to the multiparametric histopathologic prediction system suggested by Brandwein-Gensler et al., (Am J Surg Pathol 2005, 29:167-78). The total score incorporated scores of three parameters: worst pattern of invasion, perineural invasion and lymphocytic infiltration. The results were evaluated using Fisher exact test and logistic regression analysis. Results: The disease in the young group was consistently locally and regionally more advanced at diagnosis. However, the 5-year disease free and overall survival rates were similar for both groups. Salvage surgery in cases of recurrence was consistently associated with death in the old group only. Young female patients had the worst prognosis with only 20% 5-year survival, independent of initial staging or treatment strategy. Young patients showed no association with classic etiologic factors. Histologically, the total score was not significantly different between the young and old groups. The score of the worst pattern of invasion was strongly associated with regional metastases and disease recurrence (OR=9.560, p=0.001). In addition to the total score, age and gender gave perfect prediction of recurrence with exact OR=2.4 (95% CI = (1.038, 5.460), p=0.013). Conclusions: The disease in the young is usually reported to have worse prognosis compared to the old patients. The uniqueness of the present study lies in providing a larger sample, with a distinct age gap of 15 years between the young and old groups, in updating findings on the etiology, treatment, outcome and analyzing clinico-pathological correlations of the disease. We have shown that only the female patients in the young group had the worst prognosis compared to any other group of patients, treated in the same way. This is in contrast to the accepted belief that all young patients with SCC have a worse prognosis compared to the old ones. Hormonal influence may be hypothesized to have a detrimental influence on the exceedingly unfavorable disease outcome in the young female patients. The value of the histopathological score is highlighted by its predictive potential for disease recurrence. Its importance is especially pronounced in light of the possibility of favorable outcome of the disease in the young male patient treated aggressively when indicated.

**S364: GENOMIC DIFFERENCES BETWEEN SMOKING AND DRINKING PATIENTS AND NON-SMOKING AND NON-DRINKING PATIENTS WITH ORAL TONGUE CANCER**

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**Objective:** To compare the genomic differences between smoking and drinking patients and non-smoking and non-drinking patients with oral tongue cancer.

**Methods:** 114 patients with oral tongue cancer were classified into 3 smoking groups (15 patients in each group) and 3 drinking groups (15 patients in each group). DNA was extracted from formalin-fixed and paraffin-embedded samples from each group. SNPs were identified using the Illumina GoldenGate assay and the Illumina GenomeStudio software (version 1.7.2). The SNPs were then genotyped using the Illumina Infinium HD assay (version 1.0). The genomic differences between smoking and drinking patients and non-smoking and non-drinking patients were analyzed using the Illumina GenomeStudio software. P-values were calculated using the Illumina GenomeStudio software.

**Results:** There were significant differences between smoking and drinking patients and non-smoking and non-drinking patients. The genomic differences included single nucleotide polymorphisms (SNPs) that were associated with smoking and drinking. The SNPs were located in regions of the genome that were associated with the development of oral tongue cancer.

**Conclusions:** The genomic differences between smoking and drinking patients and non-smoking and non-drinking patients with oral tongue cancer were identified using the Illumina GoldenGate and Infinium HD assays. The genomic differences were associated with smoking and drinking and were located in regions of the genome that were associated with the development of oral tongue cancer.

**Background:** There has been a reported increase in the incidence of
tongue cancer, especially in a much younger population that have not been exposed to the traditional risk factors — cigarette smoking and alcohol use. The aim of this study is to identify the genomic differences between the oral tongue cancers depending upon whether the patient had a history of smoking/drinking group or not. Methods: Fresh frozen tissues from 12 patients with squamous cell carcinoma of oral tongue who underwent an operation between January 2004 to December 2006 were examined. DNA and high quality RNA was isolated from oral tongue tumors (cut to be greater than 80% tumor) and matched normal tissue from each of 6 patients with a drinking and smoking history and 6 younger patients without a drinking and smoking history was examined. Gene Expression Profiling (Affymetrix U133 Plus 2 arrays) and Array Comparative Genomic Hybridization (aCGH) using the Agilent platform were performed to analyze genome-wide alterations between these two distinct cohorts. Results: Gene expression profiling analysis was performed. Using a paired t-test, there were a total of 5,767 transcripts with p < 0.05 in the non-drinking and non-smoking patients, and 4,329 transcripts with p <= 0.05 in the drinking and smoking patients. We found that 7 genes were up-regulated and 6 genes were down-regulated in the drinking and smoking patients only; and that 6 genes were up-regulated and 10 genes were down-regulated in the non-drinking and smoking patients only. The aCGH data showed that 1p32.2-1p36.12; 3q26.31;q27.2; 3q28; 4p15.33-4p13; 5p15.32-5p15.2; 7p12.1; 9q22.2-9q21.13; 9q34.2; 11q14.1-11q12.2; 16p13.2-16p11.2; 18p11.31; 3q12-q121.1, were regions of major difference between drinker/smoker and non-drinker/smoker samples. Conclusions: Genome-wide alterations are highly heterogeneous and vary significantly between the two groups. Thus, it seems that genetic and pathway are involved in oral tongue cancers related to tobacco and alcohol use and oral tongue cancers not related to tobacco and alcohol use. However, the results obtained needs to be further validated in a larger number of oral tongue samples.

S365: ASSESSMENT OF ORAL SELF-EXAMINATION FOR EARLY DETECTION OF ORAL CANCERS AND PRECANCERS IN A HIGH-RISK RURAL POPULATION

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Background: In India, oral cancer is one of the leading cancers in either sex and the most common cause of death in men. Though 85% of oral cancers are readily visible, almost 70% present in advanced stages. A simple oral self-examination can lead to early detection and reduction in the mortality due to oral cancer. Methods: The community work was organized in two Panchayats with a population of around 40000. The health workers recruited from the local community were trained to perform oral visual examination, to identify premalignant and malignant lesions, to educate the public about oral cancer, its risk factors and about oral self-examination and also to fill up the validated questionnaire on demographic details, risk habits and their awareness on oral cancer. The people were asked to read the oral self-examination brochure and report to the oral cancer-screening clinic within 4 weeks, in case of abnormal finding. The health workers did a house-to-house survey and they referred the screen positive subjects to the clinic within 4 weeks, in case of abnormal finding. The persons exposed to the traditional risk factors — cigarette smoking and alcohol use. The aim of the current research was to evaluate a theory-driven intervention to promote early detection of oral cancer, which had been purposefully designed for the target group. Methods: Letters of invitation were sent to smokers aged between 45 and 65 years old from GP practices in South London. A group of 40 smokers agreed to take part were randomly assigned to either a leaflet group (n=30) or a one-to-one instruction group (n=30) and asked to complete a pre-intervention questionnaire which addressed their current knowledge of the steps involved in performing mouth self-examination (MSE), knowledge of symptoms and risk factors for oral cancer, intention to seek help for early signs and symptoms of oral cancer, anxiety regarding MSE and perceived confidence to perform MSE and to seek help. Participants in the leaflet group were then asked to read a leaflet on ‘how to spot mouth cancer early’, which included written instructions of how to perform MSE. Participants in the one-to-one instruction group were also asked to read the leaflet and then shown the procedure of MSE (using the same steps outlined in the leaflet) and had the opportunity to perform MSE with receipt of feedback. Participants completed a post-intervention questionnaire immediately and then after 1 month to determine the effect of the intervention. Results: Repeated measures ANOVA indicated that both the leaflet and the one-to-one instruction led to more accurate knowledge of oral cancer, decreased intention to delay seeking help for potentially malignant oral symptoms, increased intention to perform MSE, increased confidence to perform MSE and to seek help for potentially malignant oral symptoms. Importantly, neither intervention raised participants’ anxiety levels. Between-groups analyses indicated there were minimal differences between the effects of leaflet and those of the one-to-one instruction. Conclusion: The results indicate that a brief, low cost intervention may be useful tool to encourage early detection of oral cancer in high risk groups. The data has informed the development of a larger study to determine the long-term effects of the intervention.

S367: UTILIZING 5-AMINOLEVULINIC ACID AND PULSED DYE LASER FOR PHOTODYNAMIC THERAPY OF ORAL LEUKOPLAKIA

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Objective: Determine the safety and efficacy of photodynamic therapy (PDT) in the treatment of oral leukoplakia with 5-aminolevulinic acid (5-ALA) and pulsed dye laser (PDL). Methods: A total of 18 subjects, between 18-80 years old, with a confirmed diagnosis of leukoplakia with or without dysplasia, measuring at least 10 mm in diameter were enrolled in cohorts of 3 within 18 months. The lesions were photographed using a Kay videomage, before Sterile Laser treatment. Fifty microliters with 20% solution of 5-ALA, Levulan KerastickTM, (DUSA Pharmaceuticals, Inc., Valhalla, NY) were applied to the lesions, for 1 to 2 hours, by utilizing custom fixtures made from hygienic polymer. Prior to laser treatment the gauze was soaked with 20% solution of 5-ALA. The laser was delivered using a yttrium:aluminum:garnet laser operating at 595 nm and 125 milliwatts, with a 7 millimeter spot size. Split doses of 1.5J/cm2 were delivered with 20% overlap. The results indicate that a brief, low cost intervention may be useful tool to encourage early detection of oral cancer in high risk groups. The data has informed the development of a larger study to determine the long-term effects of the intervention.

Conclusions: Overall the awareness of oral cancer and its risk factors is good, but there is lack the motivation to attend the clinic. The persons referred by the health workers did not report to the screening clinic because of the stigma attached to the disease.
regression was observed. For laser radiant exposure of 8 J/cm² & 178 complete regression (CR) was observed in 2/3 and partial regression (PR, 50%-70% reduction in lesion size) in 1/3, at day-30 post treatment. The PR had extensive, thick, lesion within the oral cavity. This subject was treated again with radiant exposure of 8 J/cm² & 178, additional regression was achieved but 30-40% of lesion did not respond. CR was achieved for the other subjects treated with 8 J/cm² & 178. The laser treatments were completed within 1-3 minutes. There were no significant adverse events and only minor pain (3 out of 10) was reported during laser treatment in the safety phase of the study. Conclusions: Photodynamic therapy (PDT) with 5-Aminolevulinic Acid (5-ALA) and PDL could be use to regress oral leukoplakia. The treatment is safe and well tolerated. Thick and progress lesions require multiple treatments. An application time of 2 hours and laser radiant exposure of 8 J/cm² & 178 were found to be the best settings, in this study. The high power laser allows completing the laser therapy within 1-3 minutes. More work is underway to determine the optimal laser radiant exposure and drug application to improve the rate of complete regression.

S368: TREATMENT AND FOLLOW-UP OF ORAL DYSPLASTIC LESIONS - SYSTEMATIC REVIEW AND META-ANALYSIS T.Rattay1, J.Smith1, H.M.Mehanian2, 1Institute of Head and Neck Studies and Education, Coventry, United Kingdom

Objectives: To identify the risk of progression from oral dysplasia to malignancy, and associated risk factors (including treatment modality and behavioural factors). Based on our results, we aim to develop an evidence-based clinical management and surveillance policy. Methods Study Design: Systematic literature review and meta-analysis with criteria for identifying studies, thinking about quality and extracting data. Inclusion Criteria: Cohort or case-control studies, or randomized-controlled trials (RCTs) reporting follow-up of patients with histologically confirmed oral dysplasia. Outcome Measures: Malignant transformation rate, time interval to malignant transformation, effect of clinical risk factors, such as smoking, alcohol. Results were subdivided by histological grade and treatment modality, where available. Data Collection: Using selection criteria, we identified published data by electronic database searching of MEDLINE, CINAHL, PUBMED and COCHRANE. The quality of studies and extracted data was independently assessed by two authors. Statistical Analysis: Funnel plot, random effects logistic regression model to estimate underlying mean and effect of dysplasia grade and clinical risk factors. Results: Database search revealed a total of 935 publications, of which 30 were identified. Using a meta-analysis, we included four trials. Conclusions: The malignant transformation rate was 11.5% for severe dysplasia, compared to 30.1% for severe dysplasia and carcinoma in situ (CIS) (p = 0.0001). Patients whose lesions were not surgically excised or treated medically reported considerably higher overall transformation rates than patients who underwent surgical excision (16.6 % versus 6.3 %, p=0.02). Subgroup analysis by histological grade shows a trend to earlier transformation, but no significant difference. Smoking, alcohol and site of lesions were evaluated in 4 studies in total. Data on these risk factors was insufficient for statistical purposes. Conclusions: Oral dysplasia carries a significant rate of transformation to cancer. Our results suggest the need for excision and continued surveillance, especially for high grade dysplastic lesions. There is a need for better strategies for follow-up and malignant risk quantification, including the use of molecular markers

S369: A FOOD-BASED APPROACH TO ORAL CANCER CHEMO-PREVENTION C.M Weghorst1, B.C.Casto1, T.J.Knobloch1, B.M.Warner1, Z.Tao1, G.D. Stoner1, S.K. Clinton1, E.Ozer1, D.E.Schuller1, A.Agrawal1, 1The Ohio State University, Columbus, OH

Objective: To explore the chemopreventive potential of black raspberries and strawberries on oral cancer development. Methods: Several preclinical studies were performed utilizing the hamster cheek pouch (HCP) model of oral cancer to assess the anti-tumor potential of black raspberries and strawberries. First, employing a Complete Chemoprevention Assay (CCA), male Syrian Golden hamsters, 3-4 weeks of age, were fed 5% and 10% lyophilized black raspberries (LBR) or strawberries (LS) in the diet for up to 2 weeks prior to treatment with 0.2% 7,12-dimethylbenz(a)anthracene (DMBA) in dimethylsulfoxide and for 10 weeks thereafter. Hamster cheek pouches (HCPs) were painted 3X/week for six weeks. The animals were sacrificed 12-13 weeks from the beginning of DMBA treatment and the number and volume of tumors (mm³) determined. Second, employing a Post-Initiation Assay (PAI), HCPs were treated with 0.2% DMBA for 6 weeks to initiate oral tumorigenesis. Then, 0.1 mL of 10% LBR (10 mg/application) in a 1:1 mixture of Saliva Substitute (Roxane Laboratories) and 2% methylcellulose was applied topically 3X/week for 6 weeks to one HCP. The contralateral HCP of the same animal was treated with 0.1 mL of vehicle alone. In a second PAI study, animals previously treated with DMBA for 6 wks received pellets containing either 5% or 10% LS in their diet for 6 weeks. Animals were sacrificed at 12 weeks to examine the effects of LS on tumor incidence and multiplicity. Results: Complete Chemoprevention Assays: LBR (dietary) and LS (dietary) maximally and significantly reduced the number of oral tumors by 44% and 41%, respectively. LS significantly reduced the number of oral tumors by 30% for 6 weeks treatment. Conclusions: Dietary and topical administration of black raspberries and strawberries dramatically reduce oral cancer development in the hamster cheek pouch. We have recently translated these striking animal model findings into two phase II clinical chemoprevention clinical trials. First, in the Pre-surgical Model trial, biopsy-confirmed oral cancer patients were given LBR troches (~ 1gm 4x/day) between their time of diagnosis and subsequent surgery. Baseline, pre-treatment biopsies of tumor and distant normal tissues were compared to corresponding tissues obtained at surgery (post-treatment/LBR-exposed). Global gene expression changes revealed by Affymetrix GeneChip analysis generated a consensus, clinical LBR-responsive, gene expression profile of the oral cancer microenvironment. Second, in the Post-surgical Model trial, oral cancer patients are being given LBR troches 4x/day for six months following surgical resection. These patients will be evaluated for locoregional recurrence or second primary tumors at routine standard of care appointments. These latter studies will clinically assess the potential of long-term LBR treatment to inhibit, delay, or reverse the incidence of oral cancer recurrence and/or second primary oral lesion development.

TRANSLATIONAL: MEDICAL ONCOLOGY/GENE THERAPIES

S370: METRONOMIC ADMINISTRATION OF SMALL MOLECULE INHIBITOR OF BCL-2 COMBINED WITH CISPLATIN IN XENOGRAFTED HEAD & NECK CANCER N.Ashimori1, B.D.Zeitlin1, A.Spalding1, LE.Nor1, 1University of Michigan, Ann Arbor, MI

Bcl-2 is an anti-apoptotic protein that is upregulated in several tumor types, and its expression levels have strong correlation to the development of resistance to therapy and poor prognosis. We have recently demonstrated that Bcl-2 also functions as a pro-angiogenic signaling molecule, and that Bcl-2 expression is upregulated (~ 60,000 fold) in the endothelial cells of human head and neck tumors as compared to endothelial cells of normal oral mucosa. In vitro and in vivo, TW-37 and Cisplatin synergized in inducing cytotoxicity in HDMEC and the head and neck cancer cells. The objective of this work was to evaluate the anti-angiogenic and anti-tumor effect of a novel small molecule inhibitor of Bcl-2 (TW-37) when used by itself, or in combination with Cisplatin. Methods: Sulforhodamine B (SRB) assay and propidium iodide staining followed by flow cytometry were used to characterize the cytotoxicity of TW-37 and/or Cisplatin in human dermal microvascular endothelial cells (HDMEC) and in a panel of head and neck tumor cells (i.e. OSCC3, UM-SCC-11A, UM-SCC-74A) in vitro. In addition, the effect of drug concentration, and sequence of treatment were also evaluated by SRB assays using the same cell models. Human xenografted tumors vascularized with functional human blood vessels were developed in the SCID Mouse Model of Human Angiogenesis to evaluate the effects of single drug or combination therapy with TW-37 and Cisplatin in vivo. Results: We observed that combination therapy with TW-37 and Cisplatin was more effective than single drug treatment in inducing cytotoxicity in HDMEC and the head and neck cancer cells evaluated here. Indeed, the effect of combination of TW-37 and Cisplatin was synergistic. Interestingly, combination treatment was more effective in rapidly proliferating cells than in quiescent cells. In vivo, combination therapy with TW-37 and Cisplatin was more effective than single drug treatment in inhibiting tumor progression, and resulted in increased animal survival. Notably, the metronomic regimen with TW-37 did not result in significant systemic toxicity, as judged by the maintenance of animal weight throughout the experimental period. Conclusions: We conclude that metronomic administration of a small molecule inhibitor of Bcl-2 synergizes with Cisplatin and results in a marked inhibition of xenografted head and neck tumor progression. These results suggest that patients with head and neck cancer might benefit from a treatment strategy that includes therapeutic...
Platinum-based protocols in HNSCC are often limited by the resistance and finding ways to treat cisplatin resistant cells is an important goal for HNSCC therapy. Methods: Cisplatin resistant UM-SCC-PT cells were assessed for growth inhibition/chemosensitivity to either JSI-124, cisplatin or a combination of the two drugs by MTT assay using a 5-day continuous exposure to each drug or vehicle control. Cytotoxicity following exposure to 50nM JSI-124, 10 microM cisplatin or a combination treatment was assessed by trypan blue exclusion assays. To measure apoptosis, cells were either analyzed by Annexin-V-FITC conjugate antibody and Hoechst (Live/Dead) staining by flow cytometry or by a caspase-3 activa- tion assay (Promega) after a continuous 48 hour exposure to the drugs. Finally, treated cells were imaged with a Zeissconfocal microscope following staining with a rabbit anti-phospho-STAT3 (Y705, Cell Signaling), an anti-rabbit-647 conjugate secondary (Invitrogen) and DAPI staining of the nucleus. qPCR was used to measure levels of mRNA transcript expression using standard cycling conditions. Primer sets are available upon request. Results: MTT chemosensitivity assays demonstrated 50% growth inhibition of UM-SCC-PT cells at a dose of at 178.3 nM JSI-124. As compared to cisplatin alone, the combination of 50nM JSI-124 with varying doses of cis- platin significantly inhibited the growth of UM-SCC-PT cells (MTT assay). Likewise, trypan blue dye assays demonstrated 27% loss of cell viability following 10 microM cisplatin and a 29% loss of cell viability following 50nM JSI-124 at 48 hours, while a combination of the two drugs resulted in >50% increase in trypan blue dye staining. Exposure of UM-SCC-PT to 50nM JSI-124 produced an increase in caspase-3 activity and greater than 20% Annexin-V staining after 48 hours as compared to vehicle control. Interestingly, combination treatment of JSI-124 with cisplatin increased caspase-3 activity 4-fold over vehicle control or cisplatin alone and the combi- nation enhanced Annexin-V staining to approximately 71%. Confocal microscopy was used to simultaneously assess changes in STAT3 phospho- rylation (Ty705) and cell morphology. Treatment of UM-SCC-PT cells with 50nM JSI-124 led to decreased phospho-STAT3 staining and apoptotic morphology (membrane blebbing). Quantitative PCR analysis of mRNA expression in UM-SCC-PT cells 6-hours after treatment with cisplatin revealed increased in EGF, STAT3, BCL-XL and survivin expression. In contrast, treat- ment of UM-SCC-PT cells with JSI-124 induced STAT3 mRNA, but not EGF or BCL-XL expression suggesting that feedback loops enhanced STAT3 transcrip- tion while JSI-124 blocked the protein’s activity (demonstrated by decreased expression of the STAT3 target gene, survivin). Conclusion: Our work demonstrated that inhibiting the EGF pathway with a STAT3 inhibitor can sensitize cells to cisplatin. Unexpectedly, analysis of mRNA expression revealed that inhibition of STAT3 function led to an induction of STAT3 mRNA expression at only 6 hours. However, because activated STAT3 (Phospho-Y705) could not translocate to the nucleus, the proliferative advantage of EGF/STAT3 signaling was abrogated and cisplatin-induced apoptosis was significantly enhanced. Thus, this work demonstrates that JAK/STAT inhibitors may enhance the efficacy of cisplatin in head and neck cancers.

S372: SENSITIZATION OF SQUAMOUS CELL CARCINOMA TO CIS- PLATIN IS POTENTIATED BY SOY ISOFAVONE I.M. Pereira 1, O.E. Tuluyan 2, L. Varghese 1, S. Ali 2, O. Kucuk 3, F.H. Sarkar 2, T. Career 3, G. Wolf 1, Karmarnos Cancer Center, Detroit, MI; 2Karmanos Cancer Center, Detroit, MI; 3Department of Otolaryngology - University of Michigan, Ann Arbor, MI

Cisplatin is the most active drug used in head and neck cancer treatment. However, resistance to cisplatin leads to treatment failure in many patients. This study investigated the potential role of isoflavone (a mixture of genis- ten and diadzein) in chemosensitization of head and neck cancer cells to cisplatin. Genistin is a soy isoflavone, which inhibits protein tyrosine kinase and topoisomerase activity with potential anti-neoplastic effects. In this study, cisplatin-sensitive (UMSCC 5) and resistant (UMSCC 5 PT) cells were used to investigate their sensitization to cisplatin by soy isoflavones. The cells were treated with cisplatin, soy isoflavone, and a combination of the two. Cell growth inhibition assays, apoptosis assays, and electrophoretic mobility shift assays (EMSA) for assessing the DNA binding activity of NF-κB were conducted. The cell growth inhibition assay showed a significa- ntly greater growth inhibition in the cells treated with the combination than the ones treated with cisplatin or soy isoflavones alone. The difference was even more significant in the cisplatin-resistant cells. The EMSA displayed increased NF-κB DNA binding activity in the resistant cells, and also an inactivation of the NF-κB DNA binding activity with the use of soy isoflavones. The results of this study show that soy isoflavones, when combined with cisplatin, can improve growth inhibition of cells that are resistant to cisplatin, and the mechanism of action can be attributed to the inactiva- tion of NF-κB.
S376: ASSESSMENT OF EGFR INHIBITION BY ERLOTINIB IN TUMORS AS COMPARED TO NORMAL MUCOSA IN ORAL CAVITY SQUAMOUS CELL CA

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Purpose: Late pharyngeal toxicity has been recognized as the main obstacle in improving outcome in head and neck cancer. Molecular-targeted therapies may potentially increase the therapeutic index by differential EGFR inhibition between tumors compared to normal mucosa. This has not been demonstrated in any clinical study to date. Potential predictors of responsiveness to small molecule EGFR-tyrosine kinase inhibitor may select those patients more likely to respond to therapy. We have initiated a study to address these issues in patients with oral cavity squamous cell carcinoma (OCCSCC).

Methods and Materials: Patients with primary or recurrent OCCSCC requiring surgical resection, had normal mucosa and tumor biopsies prior to a test course of erlotinib. Patients then received one week of erlotinib 150 mg qd with the last dose given 8-12 hours prior to surgery. Repeat tumor and normal mucosal biopsies were then obtained at the time of surgical resection to evaluate the effect of the EGFR inhibitor on both the tumor and the normal mucosa. Changes in known markers of EGFR activity (such as phospho and total EGFR, ERK1/2, AKT, STAT3) were measured by immunoblotting assays. In addition, changes in distribution of these possible biomarkers were analyzed by means of a tissue microarray.

Results: Tumor specimens showed over-expression of both phospho and total forms of EGFR. Erlotinib treatment led to complete inhibition of pEGFR and also reduced EGFR expression dramatically in tumor biopsies. In contrast, normal mucosal EGFR was not overexpressed and was either not, or only slightly, inhibited by erlotinib.

Conclusion: This selective inhibition of tumor versus normal mucosal EGFR, supports a more favorable therapeutic index with the addition of EGFR inhibitors to chemo-RT or accelerated fractionation. This novel "dual disruption" therapeutic index may be beneficial in patients with head and neck cancer.

S377: SINGLE-WALLED CARBON NANOTUBES ASSOCIATED WITH PACLITAXEL INHIBIT THE GROWTH OF HEAD AND NECK SQUAMOUS CELL TUMORS

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Background: Single-walled carbon nanotubules (SWCNTs) have unique properties that make them promising candidates for biological applications. In particular, highly oxidized ultra-short single-walled carbon nanotubes (US-SWCNTs), when functionalized with polyethylene glycol (PEG), are stable in biological media. When hydrophobic molecules, such as paclitaxel, are added to the water solutions of PEGylated ultra-short single-walled carbon nanotubes (PEG-US-SWCNTs), the PEG structures act as solubilizing tenacles that effectively sponge the molecule away from the unfavorable, aqueous environment and into the more favorable, organic PEG-US-SWCNT matrix. Therefore, PEG-US-SWCNTs can be used as vectors to deliver molecular cargo, such as paclitaxel.

Purpose: To determine the feasibility of targeting oral cancer cell lines in vitro and in vivo models, with paclitaxel-PEG-US-SWCNTs and PEG-US-SWCNTs.

Results: In vitro, tumor cell proliferation studies (MTT assay) demonstrated inhibitory effects equivalent to paclitaxel dissolved in Cremophor EL. The IC50s of paclitaxel-PEG-US-SWCNTs in three different cell lines (MDA1986, UM-SCC-1, and OSC19) were found to be identical to paclitaxel (cremophor), between 1.3 nM and 1.6 nM. In all three cell lines, paclitaxel-PEG-US-SWCNTs alone did not have any inhibitory effect observable in vitro. Following autolave sterilization, the paclitaxel-PEG-US-SWCNT solution maintained an equivalent IC50 (1.6 nM vs. 1.36 nM). The paclitaxel-PEG-US-SWCNT solution was then tested in vivo using a squamous cell carcinoma line (OSC19'-luciferase) in an orthotopic tongue model using athymic nude mice. We intravenously administered 30 mg/kg of paclitaxel-PEG-US-SWCNT solution bi-weekly. After four weeks of treatment, a significant reduction in tumor volume was seen in the paclitaxel-PEG-US-SWCNT group (3.8 mm3 + 2.9 mm3) as compared to the control group (77.8 mm3 + 47.7 mm3) which received only PBS injections. Treatment with PEG-US-SWCNTs without paclitaxel also led to a reduction of tumor burden during the study (17.5 mm3 + 9.6 mm3). In all three groups, quantitation of tumor response with luminescence (photons/sec) paralleled the reduction in tumor volumes: Control (6.31 x 107 + 4.86 x 107), PEG-US-SWCNT (2.23 x 107 + 3.86 x 107), and paclitaxel-PEG-US-SWCNT (1.67 x 107 + 1.32 x 107). Conclusions: PEG-US-SWCNTs are effectively able to solubilize the water-insoluble paclitaxel. These paclitaxel-PEG-US-SWCNTs have in vitro anti-tumor efficacy equivalent to that of paclitaxel. Treatment of oral cancer cells with paclitaxel-PEG-US-SWCNTs led to a significant in vivo anti-tumor response; even PEG-US-SWCNTs themselves proved to have an effect on tumor reduction. While delivery of PEG-US-SWCNTs, both associated and unassociated with paclitaxel, has shown to be feasible and effective in an in vivo tumor model, we are currently evaluating the toxicity and potential benefits of these nanoparticle systems.
tation and after tumors were well established. Western blot analysis and immunohistochemistry were employed to assess potential targets of sunitinib responsible for anti-tumor effects. Results: Sunitinib had potent anti-proliferative effects in vitro and appeared additive to cisplatin. The anti-proliferative effects of sunitinib were more pronounced in HNSCC cell lines than in normal non-tumorigenic cell lines. Administration of the drug in vivo significantly retarded the growth of HNSCC tumor xenografts and induced rapid regression of established tumors when dosed at 40 mg/kg/day. At this dose, animals appeared healthy and gained body weight comparable to controls. At 80 mg/kg/day, equivalent anti-tumor effects were achieved, but significant toxicity was also seen. Specifically, animals lost body weight and appeared lethargic. Potential targets of sunitinib responsible for the anti-tumor effects were examined by Western blot and immunohistochemistry. The c-KIT receptor tyrosine kinase was expressed in a number of HNSCC cell lines, but expression appeared to be heterogeneous. This heterogeneity of expression was also seen in tissue sections from primary HNSCC specimens taken from patients with this disease. Conclusions: Sunitinib has potent anti-tumor activity against HNSCC in both in vitro and in vivo models of the disease. Because this agent is already approved for clinical use in other malignancies, consideration for studies of its use in patients with HNSCC is warranted.

BASIC SCIENCE: INVASION AND METASTASES

S379: PREDICTION OF LOCAL RECURRENCE AFTER RADIOTHERAPY FOR LARYNX CARCINOMA USING TISSUE ARRAY IMMUNOHISTOCHEMISTRY

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Objective: Accurate prediction of radiotherapy response in laryngeal cancer is not possible. Apart from clinical parameters such as tumor stage and volume, a selection of multiple biomarkers interacting in different pathways could yield a robust predictive panel. Material and Method: Among patients with a primary laryngeal carcinoma irradiated in the NKI-AVL between 1985 and 1999 and from whom tissue was available for TA-IH we arrayed 83 tumors on a tissue array. After exclusion of 24 patients for various reasons, we analysed 26 patients who had a local recurrence within 2 years after diagnosis (cases) and 33 T-stage matched controls. Forty patients had a glottic carcinoma and 19 had a supraglottic carcinoma. Immunohistochemistry was performed with 14 biomarkers of which 13 could be analyzed: bcl2, BCLxL, p16, p21, p27, p53, cyclin D1, HIF1a, CA9, COX2, EGFR, Ki-67, and pRb. Results: Univariate unconditional logistic regression analysis of local recurrence within 2 years after diagnosis on the selected 13 biomarkers showed only borderline statistical significance of CA9 intensity (0.0961). A stepwise selection procedure based on sex, site, T stage as well as intensities of 12 and positivity of 13 genes resulted in a model including positivity of CA9 (OR per 10% increase 1.48, 95% CI 1.04-2.11, p=0.0297) and positivity of p21 (OR per 10% increase 1.39, 95% CI 1.003-1.93, p=0.048). It showed significant improvement in goodness of fit over the null model (likelihood ratio 12.8 at 2 degrees of freedom, p=0.0016). The Goeman global test for the positivities of 13 genes adjusted for T stage, sex and site yielded a p-value of 0.16021, with most of the (non-significant) association contributed by CA9 and COX. For the 12 intensities, the corresponding p-value was p=0.24623. The unadjusted p-values were 0.02997 (positivities) and 0.053489 (intensities), but associations were no longer significant after controlling for site. The hierarchical cluster model resulted in 3 clusters, which did not differ by their risk of recurrence. Conclusion: In laryngeal carcinoma, hypoxia and COX2 expression provided a stronger contribution to an increased risk of local recurrence after radiotherapy as compared to well-known candidate markers p53, BCL2 and cyclin D1. However, no robust radiotherapy expression profile for the prediction of cure was found in this study.

S380: EGFRVIII INDUCES HNSCC TUMOR CELL MIGRATION AND INVASION VIA ACTIVATION OF STAT3

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Objectives: EGFR variant III (EGFRVIII) is the most common EGFR alteration resulting in a distorted ligand binding region. We previously reported the expression of EGFRVIII in 42% of HNSCC where EGFRVIII increased cell proliferation in vitro and tumor volume in vivo. Moreover, EGFRVIII decreased HNSCC cell apoptosis in response to cisplatin and decreased growth inhibition following treatment with cetuximab. EGFRVIII is constitutively activated in ligand-independent manner although the mechanisms of EGFRVIII-mediated tumor progression are incompletely understood. This study was undertaken to determine the role of STAT3 in mediating tumor cell motility and invasion by EGFRVIII in HNSCC. Methods: We isolated 4 independent clones of HNSCC cell line HNSCC2a engineered to express EGFRVIII, as well as 4 vector-transfected control clones. EGFR and EGFRVIII expression were confirmed in each clone by RTPCR. Cell migration and invasion were evaluated using cell motility and Matrigel invasion assays, respectively. Phosphorylated and total STAT3 expressions were evaluated by immunoblotting. STAT3 transcriptional activity was analyzed by a luciferase reporter assay. STAT3 siRNA and a STAT3 decoy were used to downregulate or inhibit STAT3, respectively. Results: EGFRVIII-expressing HNSCC cells demonstrated increased cell migration and invasion compared to vector transfected control cells. Immunoblotting analysis showed increased expression of phosphorysotyrosine STAT3 and a luciferase reporter assay demonstrated increased activity of EGFRVIII-expressing cells and control cells by STAT3 siRNA or STAT3 decoy treatment where the degree of reduction was greater in EGFRVIII-expressing cells. Conclusions: These results suggest that EGFRVIII contributes to enhanced HNSCC tumor cell migration and invasion via activation of STAT3. EGFRVIII appears to be a plausible target in HNSCC tumors that express this altered receptor.

S381: PREVALENCE OF K-RAS CODON 12 MUTATIONS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA AND IMPACT ON CLINICAL OUTCOMES

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Background: RAS gene mutations have been shown to occur in certain malignancies and have an impact on response to treatment and overall prognosis for certain types of cancer, more specifically NSCLC. Studies of these mutations in head and neck oncology literature have shown inconsistent results. Objectives: To determine the prevalence of K-RAS codon 12 mutations in patients with locally advanced HNSCC treated with chemo-radiation therapy with/without surgery and to evaluate the impact of these mutations on loco-regional control as well as overall, disease free and distant metastasis free survival. Methods: Out of 428 consecutive patients treated with chemo-radiation therapy in our institution and followed for a median of 37 months, 199 paraffin embedded biopsy or surgical specimens were retrieved. DNA was isolated and analyzed for K-RAS mutation status by PCR and nested PCR techniques. Statistical analysis was performed using Fisher’s exact test for categorical data and Kaplan-Meier’s curves and log-rank statistics for failure times. Results: DNA extraction was successful in 197 patients. Of the 197 specimens, 3.5% presented K-RAS codon 12 mutations using a single PCR technique. For mutated cases and non-mutated cases, LRC was respectively 83 and 32% (p=0.03), DFS was 68 and 27% (p=0.12), distant metastasis free survival was 81 and 100% (p=0.50) and OS was 65 and 57% (p=0.14) at three years. Mutational status results from nested PCR are pending and will be presented at the meeting. Conclusions: K-RAS mutational status may influence failure pattern and overall aggressiveness and may influence the type of therapy offered to such patients.

S382: HEPARANASE INDUCES VEGF C LEVELS AND FACILITATES TUMOR LYMPH ANGIOGENESIS

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Objectives: Heparanase is an endoglycosidase that specifically cleaves heparan sulfate side chains, a class of glycosaminoglycans abundantly present in the extracellular matrix and on the cell surface. Heparanase activity is strongly implicated in tumor metastasis attributed to remodeling of the subepithelial and subendothelial basement membranes, resulting in dissemination of metastatic cancer cells. Moreover, heparanase up regulation was noted in an increasing number of primary human tumors, correlating with tumors larger in size, increased microvessel density, and reduced post operative survival rate, thus providing a strong clinical support for the pro-metastatic and pro-angiogenic function of the enzyme. We hypothesized
that similar to its pro-angiogenic capacity, heparanase also facilitate lymph angiogenesis. **Methods**: we utilized the D2-40 monoclonal antibody which specifically decorates lymphatic endothelial cells to study lymph angiogenesis in head and neck carcinoma, and correlated lymphatic density with clinical parameters and heparanase staining. **Results**: We provide evidence that lymph vessel density (LVD) correlates with head and neck lymph node metastasis (N-stage, p<0.007), and inversely correlates with survival (p<0.01). We found 45% of patients who were positive for PA and negative for molecular analysis (CK20, RT-PCR) to have metastatic lymph nodes. **Conclusions**: These findings suggest that heparanase play a dual role in tumor metastasis, facilitating tumor cell invasion and increasing the density of lymph vessels that mobilizes metastatic cells by inducing VEGF-C expression.

**S383: TETRA THIOMOLYBDATE INHIBITS HEAD AND NECK CANCER METASTASIS BY DECREASING TUMOR CELL INVASION AND INDUCING ANOIKIS**

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**Objective**: The metastatic spread of solid tumors is directly or indirectly responsible for most cancer-related deaths. Angiogenesis plays a critical role in tumor growth and tumor metastasis. Growing evidence suggests that tumor progression is dependant on "angiogenic phenotype" as expressed by angiogenic cytokines. Copper is a mandatory cofactor for the function of many angiogenic factors; therefore, reducing copper levels in the cellular milieu, limits the formation of new blood vessels. Previous studies from our lab and other labs have shown that tetrathiomolybdate (TM), a potent chelator of copper, lowers body stores of copper and suppresses primary tumor growth. The objective of this study was to investigate if TM treatment could inhibit head and neck cancer metastasis. **Methods**: We used two in vivo models to study the effects of TM on tumor angiogenesis and tumor metastasis. In the first study, tumor cells (OSCC-3, 1 x 10^6) and endothelial cells (HDMEC, 1 x 10^6) were mixed with 100 µl of Matrigel and were implanted subcutaneously in the flanks of SCID mice. Mice were randomized into two groups and received TM (0.7-1.0 mg/mouse) or water, respectively, by daily oral gavaging. The treatment was initiated one week prior to tumor cell inoculation and was continued until the end of the experiment. Blood samples from these animals were collected at regular intervals to monitor copper suppression. TM dose was adjusted to maintain serum CP 20% of baseline. At the end of study, tumors and lungs were harvested. Lungs from each mouse were divided into two parts. One half of each lung was paraffin embedded and processed for immunohistochemistry. The other half was processed for colony formation assay by treating with collagenase and culturing the cells with G418 (400 µg/ml) for 7 days. In the second animal model, luciferase labeled OSCC-3 cells (0.5 x 10^6) were injected in the SCID mice via the tail vein. Similar to flank model, animals were divided into two groups and treated with TM or water. Tumor metastasis to lungs was monitored weekly by in vivo bioluminescence. At the end of 6 weeks, animals were sacrificed and lungs were harvested and processed as described above. Effect of TM on tumor cell invasion was evaluated by Matrigel invasion assay. Tumor cell anoxia was evaluated by culturing tumor cells in non-adhering conditions and the tumor cells undergoing apoptosis was examined by TUNEL assay. **Results**: Animals treated with TM showed a significant decrease in tumor angiogenesis as compared to untreated controls. Similarly, TM treated animals showed significantly lower lung metastasis in both in vivo models as compared to the control group. In addition, tumor cells were collected on days 4, 8, 14, 21 and 28 and TM treated animals developed significantly smaller, less aggressive colonies and these colonies had significantly fewer tumor cells. TM treatment significantly inhibited tumor cell motility and invasive- ness and induced anoikis. **Conclusions**: With its low toxicity profile and good oral availability, TM is a strong candidate to be tested as a potential adjuvant treatment option following primary therapy, for preventing head and neck cancer metastasis.

**S384: RT-PCR FOR CYTOKERATIN 20 FOR MOLECULAR DIAGNOSIS OF LYMPHATIC METASTASES IN PATIENTS WITH HEAD AND NECK CANCER**

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**Background**: The presence of neck metastasis is an important prognostic factor for survival in squamous cell carcinoma (SCC) of oral cavity and oropharynx. Conventional techniques of pathological analysis (PA) of neck dissection specimen might have false negative. Reverse-transcriptase polymerase chain reaction (RT-PCR), which is more sensitive and less expensive than PA, may be a better diagnostic test in detection of lymphatic metastasis in SCC. Cytokeratin 20 (CK 20) has become an important tool for characterization of metastatic lymph nodes. The objective of this study was to compare the diagnosis of lymphatic metastases of SCC in sentinel lymph nodes to conventional PA in a series of patients. **Methods**: We studied 20 patients with SCC of oral cavity and oropharynx with clinically negative necks without previous treatment who underwent sentinel lymph node biopsy (SLN) using a hand-held gamma probe was evaluated by conventional PA and molecular analysis (CK20, RT-PCR). Also, a comparison was done between positive controls of tissues with known SCC and negative controls with deionized water. **Results**: Of the ten patients, six (60%) by PA and seven (70%) by molecular analysis had positive metastatic lymph nodes for SCC. Determination of CK20 gene expression by nested RT-PCR matched with positive and negative controls with 100% of sensitivity, specificity and accuracy. **Conclusions**: In this study, determination of CK20 gene expression by nested RT-PCR improved in 17% the rate of detection of lymphatic metastasis. The technique has a sensitivity, specificity and accuracy of 100% compared to positive controls of tissue with SCC and negative controls of deionized water.

**S385: PGE2 PRODUCTION IS ENHANCED IN UV EXPOSED KERATINO CYTES. EVIDENCE FOR THE ROLE OF 15-HYDROXYPROSTAGLANDIN DEHYDROGENASE**

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**Objective**: Non-melanoma skin cancer (NMSC) accounts for about half of all new cancer diagnoses in the United States and commonly occurs in the head and neck. Ultraviolet (UV) exposure has been causally linked to NMSC. However, our understanding of the mechanisms underlying UV-mediated skin carcinogenesis remains incomplete. Acute exposure to UV radiation leads to elevated levels of prostaglandins (e.g. PGE2) in the skin. Considerable evidence has accumulated suggesting a role for elevated levels of PGE2 in the pathogenesis of NMSC. PGE2 stimulates cell proliferation, angiogenesis, cell invasion, resistance to apoptosis, and immune suppression. Moreover, knocking out specific receptors (EP) for PGE2 or treatment with nonsteroidal anti-inflammatory drugs, prototypic inhibitors of PGE2 synthesis, protect against skin carcinogenesis. To date, the increase in PGE2 production observed following UV exposure has been attributed to induction of COX-2, an enzyme that contributes to increased synthesis of PGE2. Whether reduced catabolism of PGE2 also contributes to the increase in levels of PGE2 is unknown. 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is the rate-limiting enzyme for the catabolism of PGE2. Several recent studies have suggested that reduced expression of 15-PGDH contributes to the elevated levels of PGE2 found in inflamed or neoplastic tissues. Importantly, knocking out 15-PGDH in mice resulted in increased levels of PGE2 in the colonic mucosa and to enhanced formation of colon tumors consistent with its role as a tumor suppressor gene. In the current study, we investigated whether loss of 15-PGDH expression contributes to the increased production of PGE2 that is observed when keratinocytes are exposed to UV radiation. **Methods**: HaCaT cells, immortalized human keratinocytes, were treated with 0.5 µM/cm² of UV. Cells were harvested from 6-24 hours later. Western blot analysis was carried out for COX-2 and 15-PGDH. 15-PGDH enzyme activity was determined by measuring the transfer of tritium from 15(S)-[15-3H] PGE2 to glutamate. PGE2 production was measured by enzyme immunoassay. Small interfering RNA (siRNA) was used to knockdown 15-PGDH expression in HaCaT cells. **Results**: UV caused a more than 10-fold increase in PGE2 production. This occurred in association with dose- and time-dependent induction of COX-2 and suppression of 15-PGDH levels. The reduction in 15-PGDH protein levels was mirrored by decreased 15-PGDH enzyme activity. Knocking down 15-PGDH also led to increased production of PGE2. **Conclusions**: The production of PGE2 by keratinocytes upon UV exposure to UV radiation. This appears to reflect both increased synthesis due to up-regulation of COX-2 and reduced catabolism because of down-regulation of 15-PGDH. Studies are underway to define the signal transduction pathway by which UV regulates the expression of 15-PGDH and to assess the importance of this gene in mediating both the acute and chronic consequences of UV exposure.

**S386: IDENTIFICATION OF UNIQUE AND COMMON LOW ABUNDANCE TUMOR-SPECIFIC TRANSCRIPTS BY SUPPRESSION
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Human cancer is a heterogeneous disease that can vary widely in clinical outcome and therapeutic response. This heterogeneity is likely to reflect the accumulation of numerous genetic aberrations and influences of the tumour microenvironments acquired throughout the multistage progression of cancer. Various clinical and pathological characteristics have served as important tools to classify and stratify different tumour groups with respect to their prognosis and treatment outcomes. However, there is always a need to improve the resolution of such analyses. Applying genome-wide, microarray gene expression analysis to identify deregulated genes in different tumour types can provide potential gene candidates as diagnostic and prognostic tools and promising targets for drug development. However, the detection of genes with low levels of expression remains a major challenge. We have designed a strategy, termed modified suppression subtractive hybridization (mSSH), to identify genes encoding rare transcripts. The strategy entails incorporating the T7-promoter sequence at the 5'end of the non-coding cDNA strand during first strand cDNA synthesis so as to generate uni-directional anti-sense RNA from the resultant cDNA following conventional SSH. These transcripts are subsequently analyzed by Affymetrix oligonucleotide gene arrays. Four nasopharyngeal carcinoma (NPC), five hepatocellular carcinoma (HCC), and five breast carcinoma biopsies were employed separately to test the effectiveness of this protocol as drivers to enrich for low abundance tumour type-specific transcripts. The total detectable number of probe sets following mSSH was reduced by an order of magnitude of almost ten in comparison to those detected for the same resected tumor tissues without undergoing subtraction, thus yielding a subtraction efficacy of over 90%. Using this experimental approach, we have identified 83 NPC-specific, 48 HCC-specific, and 45 breast carcinoma-specific genes. In addition, 115 genes were up-regulated in all three cancer types. When compared to gene-profiling data obtained without mSSH, the majority of these identified transcripts were of low abundance in the original cancer tissues. mSSH can therefore serve as a comprehensive molecular strategy for pursuing functional genomic studies of human cancers.

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Objective: A replication-competent, attenuated, mutant oncolytic herpes simplex virus-1, OncoVEX-GALV/CD, expresses a fusogenic protein from simple virus-1, OncoVEX-GALV/CD, expresses a fusogenic protein from the adenovirus type-5 (Ad5) large T antigen, allowing the virus to bind and enter host cells more efficiently. The viral genome is deleted of the Pho-ribosyltransferase (CD/UPRT) which converts the prodrug 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU). We evaluated the ability of OncoVEX-GALV/CD to (1) directly lyse head and neck squamous carcinoma (HNSCC) cell lines, and (2) convert 5-FC to 5-FU as a strategy to enhance oncolytic therapy. Methods: Four HNSCC cell lines (QLL1, QLL2, SCC15, SCC23) were exposed to OncoVEX-GALV/CD in vitro. Viral cytotoxicity experiments were performed in the presence and absence of 5-FC. Viral cytotoxicity was determined by daily lactate dehydrogenase assays. Viral replication was confirmed with viral titers. Results: OncoVEX-GALV/CD was highly cytotoxic to all four cell lines, with greater than 80% cell death six days after exposure to virus at an MOI of 0.1. An MOI of 0.01, virus alone was cytotoxic to less than 5% of cells at six days. However, exposure to 5-FC at MOI 0.01 resulted in 9-fold enhanced cytotoxicity at these conditions. There was no detectable cytotoxicity by exposure to 5-FC alone. Conclusions: OncoVEX-GALV/CD is highly cytotoxic to head and neck squamous carcinoma cell lines QLL1, QLL2, SCC15, and SCC25 in vitro. The addition of 5-FC to low viral concentrations significantly enhances cytotoxicity through conversion to 5-FU. These results suggest that an oncolytic herpes virus designed to express a prodrug conversion enzyme may result in significantly enhanced therapy of HNSCC.

S388: CHANGING TREATMENT PARADIGMS IN THE MANAGEMENT OF SQUAMOUS CELL CARCINOMA OF THE SUPRAGLOTTIC LARYNX: S.C.Kerns1, J.Lavine1, K.Muzaffar1, C.Zender1, 1Loyola University Medical Center, Maywood, IL

Objectives/hypothesis: Squamous cell carcinoma of the supraglottic larynx is an aggressive and potentially fatal disease. Clinically it behaves much differently than cancer of the glottis due to its robust lymphatic supply and less constrained anatomical boundaries. These differences account for the increased incidence of locoregional metastasis and more advanced stage at the time of diagnosis. Over the last fifty years survival rates have remained relatively unchanged. Treatment strategies have evolved from mostly surgical modalities to non-surgical modalities which include radiation and chemoradiation. We are now seeing an increase in the surgical management of these tumors due to the advent of transoral laser surgery. The goal of this study is to compare open surgical techniques and transoral laser microsurgery in the treatment of these tumors. Study design: A retrospective, 15-year review from a tertiary care academic center. Methods: Inclusion criteria included patients with squamous cell carcinoma of the supraglottic larynx from 1990 to 2005. Age, cancer stage and prior treatment were recorded. Primary outcomes measured for each group included overall survival, disease free survival and local recurrence. Predictors evalu-
Eighty-five patients fit the inclusion criteria. We present the management and outcomes of patients treated through the retrospective review of the records of salvage surgery forms an integral part in the success of non-surgical organ preservation approaches. V.Rao1, A.Druz1, D.Chauk1, M.Despande1, P.Pai1, P.Chaturvedi1, R.Hawaldar1, Tata Memorial Hospital, Mumbai, India

Objectives: Salvage surgery forms an integral part in the success of non-surgical organ preservation strategies. Varying success rates have been reported with non-surgical organ preservation protocols in the treatment of early cancers of larynx and hypopharynx with 5-40% of patients mandating some form of salvage surgery. This study evaluates 1) Morbidity, 2) Disease control, 3) Survival 4) Neck Management as well as 5) Feasibility of salvage laryngeal surgery in salvage scenarios.

Methods: Retrospective chart review of 47 eligible patients who underwent salvage laryngeal surgery following definitive radiotherapy [standard and accelerated] with or without chemotherapy for T1-T3, N0-2 squamous carcinoma of the larynx and hypopharynx between the periods of 2003-2006 were evaluated. These patients were selected from an existing database for laryngeal surgery of 384 patients. All patients were staged using (UICC-2002). Statistical analysis was performed using SPSS software (ver. 14).

Results: Glottis comprised of (68%), supraglottis (13%), hypopharynx (19%). Definitive radiotherapy was given in 77% and concurrent chemotherapy with radiotherapy in 23%. Pre-treatment staging: T1(32%), T2(23%), T3(15%), Tx(30%). Nodal status comprised of N0(62%), N1(4%), N2(4%), N3(28%). Anterior commissure involvement was observed in 30% and 9% respectively. Local control was observed in 44% and 26% respectively. Treatment Details: The median dose of radiotherapy was 66 Gy (Range 42-70) with a median duration of 46 days. Tracheostomy was performed in 21% patients. Salvage Total laryngectomy was performed in 89% and 11% of patients underwent a salvage conservative laryngeal surgery. All patients who underwent conservative surgery had well documented pre-treatment staging and tumor mapping. Neck dissection (Bilateral level III, IV) was performed in majority of the cases (91%). Tumor Characteristics at Recurrence: Mean follow up period in this study was 27 months. Staging at recurrence was T1(19%), T2(38%), T3(38%), T4(14%). Nodal status N0(94%), N1(6%). Of the 63% of patients with initial anterior commissure involvement, 43% patients showed cartilage erosion on final histopathology. Surgical Complications: Following salvage surgery 32% patients developed fistula (22% major, 78% minor). Mean fistula healing time taken was 29 days. On analyzing the factors contributing to fistula formation none of factors (duration, dose, recurrent tumor staging, and anterior commissure) showed significant impact on fistula formation.

Voice Outcomes: When the Clinicians assessment of Voice outcome were analyzed for patients undergoing total laryngectomy it showed 1)Excellent-9%, 2)Good-65%, 3)OK-13%, 4)Poor-9% 5)Unable to speak-4%. Patterns of Failure Post Salvage: The patterns of failure included Locoregional failure(5%), distant metastasis(7.5%), and second primary(3%). The estimated overall survival for patients in this group undergoing salvage laryngectomy was 76% at 3 years. Conclusion: Salvage laryngectomy is a definite option for patients who fail treatment with non surgical organ preservation protocols with minimum impact on overall survival of the disease subtypes. Advanced age , Tracheostomy , Local recurrence as well as Compliance for follow up are imperative when embarking on salvage conservative laryngeal surgery. Role of neck dissection is mainly limited to patients with positive nodes prior to treatment. Voice outcomes following salvage laryngectomy are comparable with patients undergoing primary laryngectomy.
To assess speech and swallowing functions in patients who underwent microsurgical reconstruction of palatal and oropharyngeal defects. **Methods:** This is a retrospective study, where data was obtained on all the patients who had undergone resection of oropharynx which included at least part of the soft palate. The defects were reconstructed using free tissue transfer. 20 patients underwent such procedures in our unit between 2003 to 2007. The patients were then clinically analysed for speech and swallowing function using standardised tests and also by appropriate questionnaires. **Results:** Velopharyngeal function post-operatively ranged from poor to near normal. Palatal defects reconstructed with combination of free tissue transfer and pharyngeal flap had better function than when only free tissue transfer was used. **Conclusion:** Functional reconstruction of palatal and oropharyngeal defects remains a challenge. Soft palate reconstruction with free tissue transfer along with local pharyngeal flaps provide better velopharyngeal competence and hence better speech and swallowing.

S395: EARLY ORAL FEEDING AFTER SALVAGE LARYNGECTOMY
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**Objective:** To review the practice of initiating early oral feeding at post operative day five in salvage laryngectomy patients and the rate of pharyngocutaneous fistula formation. **Methods:** A chart review of 29 patients who underwent salvage laryngectomy at a tertiary medical center, between January 2002 and July 2007, was completed. Patients included in the study had radiation therapy +/- chemotheraphy for laryngeal squamous cell carcinoma with subsequent total laryngectomy due to incomplete response to treatment, tumor recurrence, or laryngeal necrosis. Early oral feeding was defined as oral intake on or before postoperative day five. Patients were excluded from analysis if they were reliant on a gastrostomy tube preoperatively, had a concurrent complete glossectomy, or developed a fistula prior to beginning oral feedings. Data collected included: tumor stage, total radiation dose, time interval between primary treatment and total laryngectomy, and the type of pharyngeal closure. The day oral feeds were started, the length of hospital stay, and any postoperative complications were also noted. **Results:** Twenty patients met complete inclusion criteria. Pharyngocutaneous fistula occurred in 10% (2/20) patients. Patients without postoperative complications on average remained in the hospital for 8 days. This allows for a shortened hospitalization compared to patients whom are not fed orally for 10 or more days. **Conclusions:** The risk of fistula formation is not increased, and the duration of hospital stay may be abbreviated in patients given early postoperative feeds five days after salvage laryngectomy.

S396: CONSERVATIVE MANAGEMENT OF IATROGENIC ESOPHAGEAL PERFORATION IN HEAD AND NECK CANCER PATIENTS WITH ESOPHAGEAL STRICURE
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**Objective:** To evaluate the efficacy of conservative management of iatrogenic esophageal perforation following a stricture from the treatment of head and neck cancer. **Methods:** Retrospective chart review of 24 patients with esophageal perforation treated at the Detroit Medical Center/Harper University Hospital from 1999 to 2008. Of these, 8 head and neck cancer patients had esophageal stricture with dilation and subsequent esophageal perforation. **Results:** In the cohort group, 6 were managed conservatively; 1 with thoracotomy and mediastinal exploration with drainage; 1 with esophagectomy with proximal gastrectomy. Average age of the 4 females and 4 males was 55.8 years. There were 4 females and 2 males treated conservatively. Two males were treated surgically. Of the 8 patients, all had radiation, 6 had chemotherapy, and 5 had surgery as part of their oncologic treatment. Location of the original tumor was esophagus (3), supraglottic larynx (3), right vocal cord (1), and tongue/FOM (1). Site of stricture was at the cricopharyngeus or neopharynx at 18-25 cm from the central incisors for all patients. Radiographic imaging revealed proximal penetrating injury. The patient that required esophagectomy with proximal gastrectomy had distal esophageal perforation with tracheal and bronchial fistulae. Size of perforation was estimated between 0.5 to 1.0 cm in all patients. In 7 out of the 8 patients the dilatation procedure was antegrade. Most common initial sign and symptom was tachycardia and chest pain. Chest tubes were utilized for pneumothorax and pleural effusion as part of the conservative management. All patients were kept NPO, with either enteral or parenteral nutrition. Broad spectrum IV ABX and antiflux measures was maintained throughout the hospital stay. Complications encountered were acute renal failure, mediastinitis, and MRSA pneumonia. Average number of hospital stay was 14.4 days for the conservativ group (6) and 15.5 days for the surgical group (2). Follow-up Barium or Gastrograffin swallow studies did not reveal any leakage. All 8 patients survived to be discharged from the hospital and the discharge diet was tube feedings. **Conclusion:** In head and neck cancer patients with post-treatment esophageal stricture, iatrogenic cervical
There are no established criteria to decide whether to perform a planned neck dissection following high-dose radiation therapy (RT) of head and neck cancer with curative intent. The goal of the study is to establish when signs of nodal disease seen on computed tomography (CT) of the neck after RT or chemoradiation therapy can predict the probability of residual lymph node disease in patients with cervical metastatic disease from squamous cell carcinoma of the head and neck region. Materials and Methods: We reviewed clinical records of patients with cervical metastasis from head and neck squamous cell carcinoma who underwent radical or modified neck dissection after high-dose RT for squamous cell carcinoma of the head and neck region. Twenty-two patients who had undergone a pre-RT CT scan, RT with curative intent and a post-RT CT scan, followed by neck dissection were retrospectively included in the study, for a total of twenty-four heminecks. Neck lymph nodes suspicious for metastatic involvement were identified based on the following criteria on the pre-RT CT: any nodal dimension larger than 15 mm, presence of necrosis, or extracapsular extension. Pre- and post-RT nodal volume, presence of necrosis and extracapsular extension, and nodal station were recorded for each abnormal lymph node. Percent volume changes of the lymph nodes between the pre- and post-RT CT were calculated (volume of lymph node on the pre-RT CT minus volume of the same lymph node on the post-RT CT percent). Surgical pathology reports were also reviewed for each hemineck. Spearman correlation coefficient and multiple linear regression were used for statistical analysis. Results: Fifty-nine abnormal lymph nodes were identified by imaging criteria. Average pre- vs. post-RT volume change percentages (+/- standard error of the mean) were significantly different between the fifteen nodes that were found to be positive at neck dissection (22.07% +/- 27.98%) and the forty-four lymph nodes that were found free of disease (69.07% +/- 3.34%) (p < 0.001). Intra- and inter-observer variations in the decision to perform neck dissection were assessed. Results of logistic regression analysis showed that sensitivity of CT seems to be 100% for persistant nodal disease. It appears extracapsular spread on any CT scan or necrosis on post-RT CT, since the extracapsular spread in the lymph node is not accurately evaluated in the pathologic evaluation and in only 25% of the benign lymph nodes (P < 0.001). 100% of positive nodes and only 44% of negative nodal disease had either necrosis on post-RT CT or signs of extracapsular spread on pre- and post-RT CT. Conclusions: Our data indicate that CT findings may help predict the likelihood of residual nodal disease in patients with squamous cell carcinoma of the head and neck treated with high-dose RT. Planned post-RT neck dissection is recommended in patients with signs of extracapsular spread on any CT scan or necrosis on post-RT CT, since the sensitivity of neck CT seems to be 100% for persistent nodal disease. It appears that neck dissection may not be needed in patients without these CT findings.

**Purpose:**

Three techniques using IMRT were compared on the treatment of head and neck tumors as commonly employed: (A) extended-field IMRT with a single isocenter to treat the entire target volume; (B) a three field method using IMRT to treat the primary tumor matched with conventional opposed laterals and an AP field to treat the upper and lower neck, respectively; (C) a two field method using IMRT to treat the primary and upper neck matched with an AP field for the low neck supracavicular fossa. Beam-split techniques used in the latter two approaches reduce dosimetric uncertainties at the matchline and allow IMRT to the upper neck with more precise calibration of the independent jaw or MLc used to produce the beam-split. The objective of this study is to evaluate the potential matchline dose variation if such a systematic error occurs. Materials/Methods: Plans were generated using a commercial treatment planning system, which allows the combination of conventional and IMRT fields in one plan. Oropharynx and nasopharynx cancer patients were selected for analysis of the two field (2F) and three field (3F) approaches, respectively. A midline cord block was used in the AP supraclavicular fields. To simulate the effect of a systematic error in jaw/MLc placement, analyses were performed with the conventional fields matched exactly and shifted 1.2-3 mm (superior-inferior) relative to the IMRT fields. Dose covering 95% of the tumor volume (D95), maximum point dose (Dmax), and maximum dose encompassing 1 cc (D1cc) were measured for a 1.2cm thick volume of the CTV centered at the matchline (mCTV) to assess tumor volume dose heterogeneity and coverage. The spinal cord was the only critical structure near the matchline for both approaches. Spinal cord Dmax and D1cc for the mCTV within the IMRT fields were analyzed. Results: For the 3F approach, overlap of the opposed laterals with the IMRT fields led to a concerning increase in spinal cord Dmax (3.2,1mm - 17%, 6%, 1%) and D1cc (6%, 5%, 4%). A gap between the opposed laterals and the IMRT fields led to a significant underdosing of mCTV [D95 decreased by 14.3Gy(25%), 9.0Gy(16%), 4.0Gy(7%)] . In the 2F approach, the midline cord block adequately protected the spinal cord in all degrees of overlap with a negligible change in D1cc (<0.5%). A gap again led to a significant underdosing of the mCTV [D95 decreased by 10Gy(20%), 3.3Gy(6%), 2.9Gy(6%)]. This underdose is especially concerning with the 2F approach because placement of the matchline is usually dictated by the maximum IMRT field length, often necessitating a split over positive neck nodes (considered part of the GTV). The 3F approach is not typically limited by IMRT field length, thus it is rarely necessary to split over GTV. Conclusions: Consistent systematic errors due to independent jaw/MLc misalignment can potentially lead to concerning dosimetric variations when matching conventional and IMRT fields in head and neck radiotherapy. When present, they may seriously compromise local control and lead to matchline failures. Spinal cord tolerance may also be exceeded.

**Aims:** Reirradiation of local-regional recurrence (LRR) of HNSCC has been reported to achieve long term disease control in some patients. However, due to toxicity and unknown pattern of failure there is uncertainty regarding optimal treatment fields/treatment volumes and dosage. In order to establish a treatment guideline we reviewed our curative-intent reirradiation cases. Focusing on failure patterns and toxicity. Methods: We retrospectively reviewed files and treatment plans of all patients who underwent curative-intent reirradiation for non-resectable recurrent HNSCC at our institution and who had minimal follow-up of 6 month. Results: 66 patients with patient progression during treatment, to 74 Gy). In all re-irradiation cases the radiation volume was restricted to the gross tumor volume (GTV) with tight margins (0.5-1.0 cm). Forty seven of the patients received concomitant chemotherapy. At a median follow up of 41.7 month, 44 (67%) patient died and 22(33%) are alive, of whom 16 (23%) are free of disease. Kaplan-Meier estimate of overall survival and disease-free survival (DFS) at two years are 40.1% and 27.4% respectively and at 5 years 27% and 22% respectively. Fifty of the patients (77%) had a third recurrence or persistent disease. 32 patients had an isolated LRR, and 15 had both LRR and distant metastasis (most commonly brain and lung). 3 patients had isolated distant metastasis (2 lung, one bone). In 45 patients the LRR occurred within the reirradiated GTV and in two patients (3.3%) isolated LRR was outside the reirradiated GTV. [95% CI 0.1-0.4]. Severe acute complications consisted of aspiration and arytenoid edema in one patient each. Nineteen patient (29%) have severe late complication including 12 (18%) long term feeding tube dependency, 2 patients with carotid blow out necessitating salvage surgery (both eventually died from advanced neck disease), 2 patients with laryngeal chondronecrosis.
Patients with T4 laryngeal/hypopharyngeal SCC are poor Despite several studies detailing long-term results of the treatment, and follow-up were recorded. The primary study endpoints were NED at 26 months and the 4 other patients are doing well from 6 months to 18 months. Conclude: Although radical radiation to upper aerodigestive tree is associated with high rate of tumor control, but at a price of major quality of life impairment. A new treatment paradigm is under study. Methods: Review of our data base of patients with unknown primary head and neck squamous cancer revealed 54 patients of whom 46 had SCC nodal disease. Radical radiation +/- surgical resection was given to 39 patients (85%). Results: Long term survival was 54% (mean follow up of 37 months). Local recurrence (tumor re-appearance) occurred in 13%, distant failure in 7%. Major complications of therapy occurred in 20%. The latter included xerostomia (5 patients), esophageal stricture (1 patient), carotid rupture (1 patient), brachial, plexopathy/fibrosis of shoulder (3 patients). We have initiated a pilot study of neoadjuvant chemotherapy (without primary radiation) with subsequent neck dissection and selective site radiation for extra nodal disease. One of 5 patients treated developed a reappearance of tumor at base of tongue at 16 months, and responded to surgical resection and radiation to primary site. Patient is NED at 26 months and the other patients are doing well from 6 months to 18 months. Conclude: Although radical radiation to potential primary site(s) is considered standard of care, we believe a new treatment paradigm is warranted. Neoadjuvant chemothera- py with neck dissection and selective radiation therapy, and continued primary site observation appears to be a reasonable treatment alternative. S401: RADIOTHERAPY AS SINGLE-MODALITY THERAPY FOR HEAD AND NECK PARAGANGLIOMAS: TWENTY-TWO YEAR RESULTS FROM A SINGLE CENTER K. Otto1, J. Franklin1, D. Goldstein1, P.J. Gullane1, B. Cummings1, 1University of Toronto, Toronto, ON, Canada; 2University of Western Ontario, London, ON, Canada Objective: Despite several studies detailing long-term results of the treatment of head and neck paragangliomas, no uniform consensus exists on the best treatment for these lesions. The benefits of surgical management, standard in many centers, must be weighed against the risks of cranial nerve deficit, life-threatening hemorrhage, or cerebrovascular accident. Radiotherapy (both standard external beam radiotherapy (EBRT) and stereotactic radiotherapy (SRT)), also widely utilized, has been criticized for its variable efficacy and tumor control, risk of long-term toxicity, and risk of radiation-induced malignancy. We present the long-term results from a single institution of radiotherapy as a single treatment modality for paragangliomas of the head and neck. Methods: A retrospective review was performed of all patients presenting with head and neck paragangliomas, to a tertiary-care, multidisciplinary, academic center, in a twenty-two year period from 1980-2002. Details of the tumor location, diagnosis, imaging, treatment, and follow-up were recorded. The primary study endpoints included radiologic evidence of tumor control, symptom control, and toxicity. Results: 84 head and neck paragangliomas were identified, of which, 42 were treated with single-modality radiotherapy (EBRT or SRT). Tumors of the glomus jugulare composed the largest subgroup (61.9%). Among the other diagnoses were carotid body tumors (10.7%), glomus vagale (14.3%), glomus tympanicum (4.8%), and thoracic inlet paragangliomas (2.4%). Patients were treated with a median of 36.8 (range 26-51) gray over a mean of 16 (range 13-25) fractions. 38 patients (90.5%) had radiographic stability of the lesion at the last follow-up. 32 patients (76.2%) were symptomatically stable at last follow-up, and 6 patients (14.3%) noted symptom improve- ment. The mean duration of follow-up was 98.2 months (range 5-250 months). The ten-year radiographic tumor-control rate was 89% (95% confidence interval 77%-99%). 23 patients (54.8%) developed some form of radiation-induced toxicity, with a mean grade of 0.69 (on a 1-4 standard radiation toxicity grading scale). 4 patients (9.5%) developed toxicity of grade 2 or higher. There were no radiation-induced malignancies identified during the study dates. Conclusion: EBRT and SRT as single-modality therapies represent safe and viable treatment options for paragangliomas of the head and neck. The toxicity rate and risk of radiation-induced malignancy are low. While determining the best treatment option for these lesions is still likely to be multi-factorial, the success and efficacy of radiation as a single-modality approaches that of previously published reports where surgical resection and multi-modality therapy was used, and has the potential to lessen long-term complications.

S402: FUNCTIONAL ORGAN PRESERVATION IN T4 LARYN- GEAL/HYPOPHARYNGEAL SQUAMOUS CELL CARCINOMA (SCC) M. Shah1, L. Kessel1, M. Smith1, A. Hao1, N. Gonik1, O. Tulumany1, J. Jacobs1, 1Wayne State University, Detroit, MI Objective: Chemoradiation has been used with success in selected cases of laryngeal/hypopharyngeal squamous cell carcinoma (SCC). While the rate of organ preservation is high in most of the T3 tumors, T4 tumors are usually excluded from the treatment study. Even when the organ is preserved, it is unclear how many of those patients have a functional larynx. This study examines the rate of functional organ preservation in T4 patients subjected to chemoradiation and their functional outcome based on the dependence of tracheostomy and feeding tubes. Methods: Retrospective study was conducted with T4 SCC larynx and larynx hypopharynx treated with chemoradiation with completion of their treatment. Exclusion criteria included patients who had previous treatment, second primaries, and/or metastasis. In the follow-up period, patients were evaluated for tracheostomy and feeding tube dependence. Results: There were 11 male and 2 female patients with age ranging from 36 to 75 years (56±12). The site of the primary tumor was larynx in 8 patients (62%) and hypopharynx in 5 patients (39%). Twelve patients were treated with concurrent therapy (cisplatin/radiation). Five patients had induction therapy with (5-FU and cisplatin) and 1 patient received induction therapy in the form of (5-FU, cisplatin and taxotere). The average follow-up was 28.7 months (3 to 100 months) and 10 out of 13 patients (77%) had follow-up period longer than 15 months. Overall, only 1 patient (8%) was decannulated and the other 12 patients (92%) remained tracheostomy dependent. Four patients (31%) had salvage laryngectomy and eventually did not require feeding tubes. Of the 9 patients who retained their larynx, only 2 patients (22%) did not require feeding tubes. Seven patients (54%) were feeding tube dependent. Conclusions: Patients with T4 laryngeal/hypopharyngeal SCC are poor candidates for organ preservation treatment. Most of the patients do not have a functional larynx and were dependent on tracheostomy and feeding tubes. Since organ preservation in these patients had virtually no benefits in terms of laryngeal function, total laryngectomy may be considered a bet- ter option for primary therapy in such patients.

S403: SWALLOWING FUNCTION AFTER INTENSITY-MODULAT- ED AND CONCOMITANT BOOST RADIATION THERAPY FOR OROPHARYNGEAL CARCINOMA A.W. Chan1, U.R. Kamat1, M. Truong1, A.S. Holman1, T.A. Goldsmith1, Massachusetts General Hospital, Harvard Medical School, Boston, MA Objective: To compare the swallowing function after intensity-modulated radiation therapy (IMRT) and concomitant boost radiation therapy (CBRT) in locally advanced oropharyngeal carcinoma. Methods: Between 1998 and 2006, 94 patients with Stage III or IV/A/B squamous cell carcinoma of the oropharynx were treated with IMRT (n = 40) or CBRT (n = 54) at our institutions. Both groups were well matched for all pre-treatment patient and tumor characteristics. IMRT consisted of 2.12 Gy/fraction/day to a total of 69.96 Gy in 6.5 weeks. CBRT consisted of concomitant boost at 1.8 Gy/fraction/day and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days to 72 Gy in 6 weeks. Ninety-five percent and 87% of patients received concurrent chemotherapy in the IMRT and CBRT groups, respectively. Percutaneous endoscopic gastrostomy tube (G-tube) was prophylactically placed in 98% and 81% of IMRT and CBRT patients, respectively. Fifty-three percent and 37% had undergone post-radiation videofluoroscopic swallow studies (VFSS) within 12 months after completion of radiation in the IMRT and CBRT groups, respectively. The median follow-up period was 34 months. Results: The actuarial local, regional, and distant metastasis-free, disease-free, and overall survival rates at 2 years were 100% vs. 96%, 97% vs. 94%, 94% vs. 90%, 87% vs. 81%, and 92% vs. 87% for IMRT and CBRT groups, respectively (p > 0.05). Fifty percent and 32% of patients had more than 10% of weight loss during radi- ation in the IMRT and CBRT groups, respectively (p = 0.08). At last follow- up, all patients were able to swallow and all were G-tube independent. There was no difference in the G-tube dependency rate in the IMRT and CBRT groups at 6 and 18 months (26% and 30% at 6 months, 6% and 7%
Previous experiences have proven that parotid irradiation is associated with the occurrence of xerostomia. In fact, mean dose radiation to parotids is a good predictor of long-term xerostomia after intensity-modulated radiation therapy (IMRT). However the absolute size of parotid volume varies with each patient. It was our impression that even with a mean dose of less than 26 Gy, some patients with small parotid volume still experienced significant xerostomia. Therefore, we evaluated the importance of parotid absolute volume needed to spare in order to minimize late salivary gland toxicity in patients treated by IMRT. Methods: We retrospectively graded xerostomia (NCI-CTC version 3.0) in patients with squamous cell carcinoma of the oropharynx treated primarily by IMRT, between December 1st 2004 and December 1st 2005, with at least 2 years follow-up. To be included, patients must have received 70 Gy in 35 fractions by parotid-sparing IMRT and had a mean dose of 26 Gy or less to one of their parotids. Patients had to receive concomitant platinum-based chemotherapy. Spared volume was defined as the volume receiving less than the definite radiation dose. Doses studied ranged from 10 to 50 Gy. Dosimetric parameters of parotids glands were reviewed. Absolute parotid volume spared, measured in cubic centimeters, was correlated to grade of xerostomia. Its variation in time was evaluated at 6, 12 and 24 months after irradiation. Results: 29 patients fit the criteria of this retrospective analysis. Tumor size was T1 for 12 patients, T2 for 12 patients, and T3 for five patients. All patients had at least one positive cervical node. At 12 and 24 months, there was a trend for less severe xerostomia in concordance with a greater absolute volume saved. This trend was even more striking between 30 and 35 Gy. At 24 months, 75% of patients who had more than 40 cc of gland spared had no xerostomia. However this trend was not present at six months follow-up. Conclusions: A mean dose of 26 Gy or less to the parotid is acknowledged in the literature as the standard to prevent xerostomia. It is our impression, based on the results presented here, that absolute parotid volume spared is also an important determinant of the severity of xerostomia that takes into account the variability between patients of absolute total parotid volumes. Sparing a minimum of 40 cc has shown to better predict less salivary gland toxicity over time.

S405: PREDICTION OF TREATMENT COMPLICATIONS IN PATIENTS WITH OROPHARYNGEAL CARCINOMA

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Objectives: Oropharyngeal cancer is typically treated with primary chemoradiotherapy, with or without surgery. Dependence on tracheostomy or gastrostomy tube are two common complications that may significantly impact the quality of life of patients receiving treatment. We sought to identify factors that may predict their occurrence. Methods: A retrospective review was conducted of all patients at a tertiary care center who received primary treatment for oropharyngeal cancer from 1997 to 2007. Data included 60 patients with squamous cell carcinoma of the oropharynx treated with radiotherapy and chemotherapy, with or without adjuvant surgery. Descriptive statistics were calculated for all health and clinical characteristics, demographics, and toxic effects that presented prior to completion of primary treatment. Results: Of 60 patients treated for oropharyngeal carcinoma, 73% were treated with chemoradiation alone. Preliminary data for the charts reviewed are as follows. Seventy-eight percent of tumors were advanced (stage III or IV) by AJCC criteria at the time of diagnosis. Among all patients studied, 32% required elective tracheostomy and 55% required gastrostomy tube placement. Of those requiring tracheostomy, laryngeal and pharyngeal edema were noted in 86% and 71%, respectively, compared with 47% and 27% in those not requiring tracheostomy. Among patients requiring gastrostomy, there was demonstrated dysphagia in 100%, mucositis in 83%, and trismus in 17%, compared with 60%, 30% and 0%, respectively, in non-gastrostomy patients. No significant contribution to gastrostomy dependence was noted for xerostomia. No instances of symptomatic aspiration, pharyngeal stenosis, velopharyngeal insufficiency, radionecrosis, anemia, or thrombocytopenia were reported for this cohort. Complications were not found to correlate with age, sex, or tumor stage. Conclusions: Laryngeal and pharyngeal edema correlate with the necessity of tracheostomy placement in patients receiving chemoradiation for oropharyngeal carcinoma. Likewise, dysphagia, mucositis, and trismus correlate with the necessity for gastrostomy tube placement. Knowledge of factors that may predict such complications has the potential to improve patient counseling toward prophylactic intervention prior to initiation of treatment.